Whole blood in prehospital damage control resuscitation

-Safety, feasibility, and logistics

Christopher Kalhagen Bjerkvig

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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The consequences of haemorrhages where the functions are not dangerously affected, do not of course, require transfusion, since other remedies will suffice. But when the danger is imminent, and the common means are ineffectual, as when a parturient woman trembles on the brink of the grave from uterine haemorrhage, or when a soldier is at the point of death from loss of blood, what reason can be alleged for not having recourse to this last hope, and for not attempting to recruit the exhausted frame and turn the ebbing tide of life.

Dr. John Henry Leacock, 1817

Scientific environment

The presented studies were performed at Haukeland University Hospital as a collaboration between the Department of Anesthesia and Intensive Care, the Department of Immunology and Transfusion Medicine, The Norwegian Naval Special Operations Commando, and The Norwegian Armed Forces Medical Services.

The collaborative efforts have been conducted in the Blood Far Forward research collaboration and influenced by the Traumatic Hemostasis and Oxygenation Research Network.

Blood Far Forward (BFF), a research program on whole blood resuscitation in austere environments, was initiated by the Norwegian Naval Special Operation Commando in 2010. Collaborators and participants today include: the Department of Immunology and Transfusion Medicine at Haukeland University Hospital, The Norwegian Armed Forces Medical Services, Norwegian Special Operation Command, and the U.S. Army Institute of Surgical Research. The original aim was to improve battlefield survival by developing a safe method for pre-hospital collection and transfusion of whole blood. The model is based on "buddy transfusion" and the field blood bank. During World War II, the U.S. established what could be termed "Field Blood Banks," where whole blood was collected from immediately available donors and used on-site immediately ("Buddy Transfusion"), stored, or delivered far forward on the battlefield for pre-hospital resuscitation. Currently, the BFF collaborative aims to further contribute to research on improving oxygen delivery and ameliorating acute traumatic coagulopathy in prehospital hemorrhagic shock resuscitation.

The Traumatic Hemostasis and Oxygenation Research (THOR) network is a multidisciplinary group of clinical, translational, and basic researchers with a common interest in improving outcomes in patients with severe traumatic injury,

allowing first responders to interact with academicians and for scientists to educate the medics and paramedics on the latest research in the field of pre-hospital resuscitation. The Remote Damage Control Resuscitation (RDCR) meetings, held annually in Norway since 2011 and sponsored by the Norwegian Naval Special Operations Command, the Norwegian Air Ambulance, and the Traumatic and Hemostasis Oxygenation Research Network, have gathered international leaders in far-forward resuscitation to find optimal strategies that address both mitigations of oxygen debt and coagulopathy in hemorrhagic shock patients.

The Norwegian Naval Special Operations Commando (NORNAVSOC)(MJK) is the Armed Forces maritime special force and is an integrated part of modern military operations. MJK operates nationally and internationally, solving tasks requiring thorough planning, quick reaction, high precision, and the ability to act independently.

The research received funding from The Norwegian Armed Forces Medical Services, the Dept. of Immunology and Transfusion Medicine, and the Dept. of Pathology and Laboratory Medicine.

The Dept. of Immunology and Transfusion Medicine at Haukeland University Hospital provided all Whole Blood units for the HEMS and facilitated all the laboratory investigations at the research lab.

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Haukeland University Hospital

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Without your contribution, Hanne Braathen, Joar Sivertsen, and Turid Helen Lunde, surely, there would have been no data, no results - no project. Thank you for your expert skills in the lab, endless positivity, and patience. Also, I deeply appreciate the expert opinions from Einar Kristoffersen.

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I sincerely appreciate the support from the Norwegian Naval Special Operations Commando. It has been a privilege working among some of the best. I admire leaders who are willing to take risks with the overall goal of improving battlefield survival.

Special thanks to Geir Arne Sunde and Jon-Kenneth Heltne for your excellent collaboration and for the opportunity to contribute to Paper IV. I would also like to thank my colleagues and the helicopter crews at the Dept. of Pre-Hospital Services and Dept of Anaesthesia and Intensive care.

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Elin Bjørnestad, you lead by example. Thank you for the opportunity and the appointment to a research position within the Department of Anaesthesia and Intensive care in a time of need.

Jörg Assmus, thank you for taking upon yourself the grim task of trying to teach an anaesthesiologist the essentials of statistics and for your support in this project.

I am also thankful for the insightful comments on drafts of my dissertation offered by Øyvind Thomassen, Kristian Furuskjeg, William Ottestad, Reidar Kvåle, Øystein Eikrem, and my father, Rolf Bjerkvig.

The influence of the THOR research network has been instrumental in shaping my academic mind. I would especially like to recognize Patrick Thompson, Jens Gløersen, and all the other participants from the special operations medic community in the annual RDCR pre-symposium. I'm not allowed to mention your names, but you know who you are.

I would also like to acknowledge my parents. Thank you for encouraging me in all of my pursuits. You are truly the most amazing parents I could have asked for, and I hope I can live up to your examples someday.

Finally, but most importantly, I would like to express my deepest love to my wife, Silje, and my children, Sverre, Solveig, and Sondre. Your patience and support have been unconditional, and for this, I am forever grateful. Thank you for putting out with a husband and father who has spent more time away from home than he ought. You remind me of what is important in life.

Bergen, January 2023

Christopher Bjerkvig

Contents

Abstract

Background

In the last two decades, resuscitation of hemorrhagic shock has undergone a paradigm shift. Modern damage control resuscitation strategies aim to improve outcomes by facilitating early hemostatic resuscitation with blood and blood products. The ultimate goal is to prevent, reverse or mitigate the severity and duration of shock and its consequences until definitive hemorrhage control can be achieved. As a result, both civilian and military EMS systems are considering whole blood for prehospital resuscitation of hemorrhagic shock. Although appealing, establishing a robust system for forward resuscitation with whole blood is challenging as several vital factors regarding safety, logistics, and implementation barriers need to be considered.

Aim

To investigate and evaluate the implementation of a pre-hospital low titer group O whole blood (LTOWB) transfusion program.

Methods

Paper I investigated the feasibility, safety, and efficacy of autologous re-infusion of warm fresh whole blood (WFWB) through an intraosseous sternal device in a prospective human comparative study. Paper II investigated the *ex vivo* quality of LTOWB during storage for up to 21 days in an airtight thermal container at a helicopter emergency medical system (HEMS) base compared to LTOWB stored in the blood bank. Paper III identified current pre-hospital blood transfusion programs, future needs, and potential obstacles in implementing LTOWB in a national survey among the medical directors of the Norwegian HEMS and Search and Rescue (SAR) helicopter bases. Finally, in a prospective observational study,

paper IV described and evaluated the implementation of a LTOWB program in one of the Norwegian HEMS services in 2015-2020.

Results

There was no evidence of hemolysis following sternal intraosseous re-infusion of whole blood. The median infusion rate was 46.2mL/min for the FAST-1 device, and the failure rate for inexperienced personnel was 9%.

Storage of LTOWB complied with the EU regulations throughout remote and in-hospital storage for 21 days. In addition, there were no significant differences in hematology variables, platelet aggregation, or viscoelastic properties between blood stored remotely and in the blood bank.

All HEMS and SAR helicopter services in Norway carry LTOWB or blood components. A majority of services have a preference for LTOWB because LTOWB enables early balanced transfusion and may have logistical benefits in time-critical emergencies. This far, four of 20 (20%) have implemented LTOWB. Blood banks and services that provide LTOWB report favorable experiences.

During the five years, the Bergen HEMS in study IV responded to 5124 patients. Seventy-two (1.4%) were transfused. Twenty patients were excluded mainly due to a lack of informed consent. Of the 52 patients, 48 received LTOWB. Forty-six (88%) were admitted to the hospital alive, and 76% of these received additional transfusions during the first 24 hours. Most patients presented with blunt trauma mechanisms (69%), followed by hemorrhage unrelated to trauma (29%). Overall 36 (69%) survived 24 hours, and 28 (54%) survived 30 days. No suspected transfusion reactions or logistical issues were reported.

Conclusion

WFWB transfusion through the IO route is safe, reliable, and provides sufficient flow for the initial resuscitation of hemorrhagic shock. Storage of LTOWB in thermal containers in a pre-hospital HEMS service is feasible and safe. Hemostatic

properties are present for up to 21 days of storage and are similar to LTOWB stored in the blood bank. HEMS services and blood banks report favorable experiences implementing and utilizing LTOWB in Norway. The logistics of LTOWB emergency transfusions are manageable and safe in a Norwegian HEMS service.

Abstract in Norwegian

Bakgrunn

De siste tiårene har det vært et paradigmeskifte i behandlingen av blødningsjokk. Skadebegrensende resuscitering har som hensikt å understøtte hemostatisk evne hos pasienten og reversere og dempe konsekvensene av sjokk slik at pasienten har tilstrekkelige fysiologiske reserver til å overleve påfølgende behandling i sykehus. Strategien baserer seg i all hovedsak på å starte tidlig behandling med blod og blodprodukter. I økende grad har sivile og militære prehospitale tjenester vurdert fullblod som et alternativ for den intiale resusciteringen av blødningsjokk. Selv om fullblod har tiltalende egenskaper er det flere utfordringer ved implementering av fullblod i et prehospitalt system. Forhold knyttet til sikkerhet, logistikk, lagring og praktisk bruk bør evalueres.

Mål

Å undersøke og evaluere implementeringen av et program for implementering av prehospitalt lavtiter gruppe O fullblod (LTOWB).

Metode

Paper I undersøkte gjennomførbarhet, sikkerheten og effektivitet av intraossøs sternal autolog re-infusjon av varmt friskt fullblod (WFWB) i en prospektiv human komparativ studie. Paper II undersøkte ex vivo kvaliteten til lav titer type O fullblod (LTOWB) under fremskutt lagring i opptil 21 dager i en lufttett temperaturregulert beholder ved en luftambulansebase sammenlignet med LTOWB lagret i blodbanken. Paper III identifiserte nåværende prehospitale blodtransfusjonsprogrammer, fremtidige behov og potensielle barriærer for implementering av LTOWB i en spørreundersøkelse blant medisinsk ansvarlige

leger ved luft og redningshelikoptertjenestene i Norge. Paper IV beskrev implementeringen av et LTOWB-transfusjonsprogram i Luftambulansetjenesten i Bergen i perioden 2015-2020 i en prospektiv observasjonsstudie.

Resultater

Det var ingen hemolyse etter sternal intraossøs re-infusjon av fullblod. Median infusjonshastighet var 46,2 ml/min for FAST-1-IO nålen, og feilraten ved innleggelse av IO tilgangen for uerfarent personell var 9 %.

Fremskutt lagring av LTOWB opptil 21 dager førte ikke til konsekvenser som kan true pasientsikkerheten. Blodet tilfredstilte EU krav i hele lagringsperioden. Det var ingen signifikante forskjeller i de hematologiske variablene, blodplateaggregering eller viskoelastiske egenskaper mellom blod lagret fremskutt og blod lagret i blodbanken.

Alle luft og redningshelikopter i Norge har blodprodukter tilgjengelig. Fire av 20 (20 %) har implementert LTOWB. Et flertall av tjenestene har en preferanse for LTOWB siden dette muliggjør tidlig balansert transfusjon og kan ha logistiske fordeler i tidskritiske situasjoner. Blodbanker som leverer LTOWB rapporterer gunstige erfaringer. I løpet av 2015-2020 responderte Luftambulansen i Bergen til 5124 pasienter. Syttito (1,4%) mottok blodtransfusjon. 52 pasientene samtykket til deltagelse i studien. Av disse fikk 48 LTOWB. Førtiseks (88 %) ble innlagt på sykehuset i live, og 76 % av disse fikk ytterligere transfusjoner i løpet av de første 24 timene. De fleste pasienter presenterte med stump skademekanikk (69 %), etterfulgt av blødninger som ikke var relatert til traumer (29 %). Totalt overlevde 36 (69%) 24 timer, og 28 (54%) overlevde 30 dager. Ingen transfusjonsreaksjoner eller logistiske problemer ble rapportert.

Konklusjon

Intraossøs infusjon av WFWB er trygt, pålitelig og gir tilstrekkelig flow for den initielle resuscitering ved blødningsjokk. Fremskutt lagring av LTOWB i Luftambulansetjenesten er gjennomførbart og trygt. Kvalitet tilfredstiller EU krav opptil 21 dagers lagring, og hemostatiske egenskaper e LTOWB sammenlingbar med LTOWB lagret i blodbanken. Luftambulansetjenestene og blodbankene som leverer LTOWB har gode erfaringer med implementering av LTOWB. Våre undersøkelser viser at implementering av et prehospitalt transfusjonsprogram med fullblod er mulig og sikkert. Det er videre behov for studier som ser på effektiviteten av fullblod sammenlignet med blodkomponenter.

List of publications

The thesis comprises the following papers, referred to by their Roman numerals:

I. Bjerkvig CK, Fosse TK, Apelseth TO, Sivertsen J, Braathen H, Eliassen HS, Guttormsen AB, Cap AP, and Strandenes G.

Emergency sternal intraosseous access for warm fresh whole blood transfusion in damage control resuscitation

J Trauma Acute Care Surg, 84: S120-S24. 2018

II. Bjerkvig CK, Sivertsen J, Braathen H, Lunde THF, Strandenes G, Assmus J, Hervig T, Cap AP, Kristoffersen EK, Fosse T, and Apelseth TO.

Cold-stored whole blood in a Norwegian emergency helicopter service: an observational study on storage conditions and product quality

Transfusion, 60: 1544-51. 2020

III. Bjerkvig CK, Strandenes G, Hervig T, Sunde GA, and Apelseth TO.

Prehospital Whole Blood Transfusion Programs in Norway

Transfus Med Hemother, 48: 324-31. 2021

IV. Sunde GA, Bjerkvig C, Bekkevold M, Kristoffersen EK, Strandenes G, Bruserud O, Apelseth TO, and Heltne JK.

Implementation of a low-titre whole blood transfusion program in a civilian helicopter emergency medical service

Scand J Trauma Resusc Emerg Med, 30: 65. 2022

Related papers not included in the thesis

Hudson AJ, Strandenes G, Bjerkvig CK, Svanevik M and Glassberg E.

Airway and ventilation management strategies for hemorrhagic shock. To tube, or not to tube, that is the question!

J Trauma Acute Care Surg, 84: S77-S82. 2018

Bjerkvig CK, Strandenes G, Eliassen HS, Spinella PC, Fosse TK, Cap AP and Ward KR.

"Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation

Transfusion, 56 Suppl 2: S182-9. 2016

Hagen KG, Strandenes G, Kristoffersen EK, Braathen H, Sivertsen J, Bjerkvig CK, Sommerfelt-Pettersen N, Aasheim IB, Lunde THF, Hervig T and Apelseth TO.

A whole blood based resuscitation strategy in civilian medical services: Experience from a Norwegian hospital in the period 2017-2020

Transfusion, 61 Suppl 1: S22-S31. 2021

Strandenes G, Sivertsen J, Bjerkvig CK, Fosse TK, Cap AP, Del Junco DJ, Kristoffersen EK, Haaverstad R, Kvalheim V, Braathen H, Lunde THF, Hervig T, Hufthammer KO, Spinella PC and Apelseth TO.

A Pilot Trial of Platelets Stored Cold versus at Room Temperature for Complex Cardiothoracic Surgery

Anesthesiology, 133: 1173-83. 2020

Woolley T, Thompson P, Kirkman E, Reed R, Ausset S, Beckett A, Bjerkvig C, Cap AP, Coats T, Cohen M, Despasquale M, Dorlac W, Doughty H, Dutton R, Eastridge B, Glassberg E, Hudson A, Jenkins D, Keenan S, Martinaud C, Miles E, Moore E, Nordmann G, Prat N, Rappold J, Reade MC, Rees P, Rickard R, Schreiber M, Shackelford S, Skogran Eliassen H, Smith J, Smith M, Spinella P, Strandenes G, Ward K, Watts S, White N and Williams S.

Trauma Hemostasis and Oxygenation Research Network position paper on the role of hypotensive resuscitation as part of remote damage control resuscitation

J Trauma Acute Care Surg, 84: S3-S13. 2018

Cap AP, Pidcoke HF, DePasquale M, Rappold JF, Glassberg E, Eliassen HS, Bjerkvig CK, Fosse TK, Kane S, Thompson P, Sikorski R, Miles E, Fisher A, Ward KR, Spinella PC mad Strandenes G.

Blood far forward: Time to get moving!

J Trauma Acute Care Surg, 78: S2-6. 2015

Abbreviations

ADP	Adenosine Diphosphate
ATC	Acute Traumatic Coagulopathy
ATLS	Advanced Trauma Life Support
BCT	Blood Component Transfusion
CNS	Central Nervous System
CWB	Cold Whole Blood
FDP	Freeze-Dried Plasma
FFP	Fresh Frozen Plasma
GCS	Glasgow Coma Scale
GD	Goal Directed
Hb	Hemoglobin
HEMS	Helicopter Emergency Medical Service
ICU	Intensive Care Unit
IO	Intraosseous
IV	Intravenous
LDH	Lactate Dehydrogenase
LTOWB	Low Titer Group O Whole Blood
MTF	Medical Treatment Facility
NACA	National Advisory Committee on Aeronautics
PLT	Platelets
PRBC	Packed Red Blood Cells

RDCR	Remote Damage Control Resuscitation
SAR	Search And Rescue
TACO	Transfusion Related Circulatory Overload
TCCC	Tactical Combat Casualty Care
TEG	Thromboelastography
TIC	Trauma Induced Coagulopathy
TRALI	Transfusion Related Acute Lung Injury
TRAP	Thrombin Receptor Activating Peptide
VET	Viscoelastic Testing
WB	Whole Blood
WBC	White Blood Cell
WFWB	Warm Fresh Whole Blood

1. Introduction

1.1. Trauma epidemiology and life-threatening hemorrhage

Death from hemorrhage is a significant global challenge and a considerable health burden, with more than 1.9 million deaths yearly worldwide (1). The causes of hemorrhage leading to shock vary widely and include bleeding following trauma, maternal/obstetric hemorrhage, gastrointestinal bleeding, and hemorrhage following great vessel disease (e.g., ruptured aortic aneurysm).

Trauma remains globally the leading cause of death in the population aged 0-45 years (2). In Norway, 1951 people died from trauma in 2021 (3). From a public health perspective, trauma-related injuries represent an annual cost of more than $406 billion in medical care and lost productivity in the United States (4). Understanding the epidemiology of death after trauma is vital to improving outcomes in this population. In 1983, Donald D. Trunkey published one of the most influential papers in traumatology. He described the chronological distribution of mortality and injury patterns after trauma - leading to the concept of the trimodal distribution of trauma deaths - immediate, early, and late (5).

Trunkey described that the immediate deaths, within one hour post-injury, were caused by massive injuries to the whole body, central nervous system (CNS), heart, great vessels, and compromised airways. These deaths were considered non-preventable. From a trauma systems perspective, these deaths are best addressed through injury prevention and safety programs. Early deaths (second peak) were primarily attributed to CNS injury or uncontrollable hemorrhage within one to four hours after injury. Although options for addressing primary CNS injuries are limited, efforts focus on optimizing brain perfusion to minimize secondary ischemic brain injury. Some of the deaths due to hemorrhage during this interval

are potentially preventable, emphasizing opportunities for novel interventions. The third peak corresponds to the patients who die from infection and/or multi-organ failure after days or weeks.

Trunkey´s findings have paved the way for new injury prevention concepts, the focus on expedited evacuation, and newer optimized acute therapeutic interventions that characterize trauma systems today.

Due to the advancements of the trauma systems in the early 2000s, the distribution of trauma deaths is no longer trimodal but rather bimodal, with immediate and late deaths, with a reduction in early deaths. This may reflect the improvements in the trauma systems, such as shorter on-scene times, advances in trauma and ICU care, and adherence to modern damage control principles (6). However, the proportion of early deaths still represents a major burden across several trauma systems (7, 8). This relates particularly to deaths caused by non-compressible torso hemorrhage and extremity trauma. Hence, death after trauma is mostly an acute phenomenon occurring within the timeframe of acute medical care from prehospital medical emergency services (9). One hour has frequently been suggested as a goal for initiating critical interventions. In recent years this «golden hour» doctrine has been a hallmark in most trauma systems, both within the military and civilian sectors (7, 10, 11, 12). However, defining «preventable death» has been difficult. Although several methods exist, there is no standard definition that is universally acceptable. Regardless of the metrics used, hemorrhage seems to be a consistent pathophysiological parameter associated with preventable trauma mortality. In a large autopsy study of battlefield deaths, Eastridge et al. found that 87% died before arrival at the medical treatment facility (MTF). Among these, 24% of the deaths were considered potentially preventable. Further evaluation identified that the site of lethal bleeding was mainly torso hemorrhage (67%) followed by junctional (19%) (areas at the junction of the trunk and its appendages) and extremity bleeding (14%) (13). In civilian trauma deaths, where blunt mechanisms

of injury are more prevalent, studies demonstrate that hemorrhage is the most important contributor to early deaths. One large study showed that 29% of prehospital trauma deaths were potentially preventable; of these, 64% were entirely or partially due to hemorrhage and hemorrhagic shock (10). The main focus over the last decades has thus been to achieve early hemorrhage control through damage control resuscitation.

The incidence of non-traumatic hemorrhagic shock is less evident. Holler et al. found inadequate evidence to establish precise estimates of the characteristics of non-traumatic hypotension and shock. They found that 1-2% of the emergency medical system (EMS) contacts presented with shock unrelated to trauma (14). Further, a Danish study reported that trauma victims only accounted for 35.9% of the patients who received blood transfusions from the EMS. Comparative analysis between the trauma and non-trauma victims demonstrated that the non-trauma victims were significantly older and had different hospital courses, mortality, and admission characteristics. The non-trauma patients presented with a wide variety of surgical and medical conditions, with gastrointestinal bleeding being the most prevalent (15). Hence, this heterogeneous group is a significant challenge for civilian prehospital services. Most patients are critically ill and have a mortality rate similar to trauma patients (16).

1.2. History of hemorrhagic shock resuscitation

Ancient times

The ancient Edwin Smith papyrus is the oldest known treatise on trauma care. Although it dates to c.1600BC, it is believed to be an incomplete copy of an older reference manuscript from the Old Kingdom in 2500-3000BC. It describes various treatment modalities, such as sutures, splints, and bandages to stop bleeding (17).

Homer described the treatment of war wounds in 1200 BC and emphasized the importance of surgeons on the battlefield (18). During the Roman wars, Romans deployed a combat surgeon within every legion and provided a surgical hospital at every legion fort - the first medical treatment facilities. Although treating wounds was important, the understanding of what caused death was vague except for the acknowledgment of fatal bleeding. Before the 1600s, there was no established understanding of the circulatory system. It was assumed that the blood was produced in the liver and consumed in the peripheries. This understanding was based on the works by Galen of Pergamon (AD 129-216), who made important discoveries in the field of anatomy but incorrectly assumed that bodily functions were dependent on the levels of the four humors, leading to the belief that hemorrhage was one of the conditions that benefitted from bloodletting (19).

17th century - anatomic and physiologic breakthrough

The Galenic era ended in 1628, when William Harvey, an English physician, published his seminal discoveries that blood flowed away from the heart and returned in the veins, meaning that the blood circulated (20). Further, he stated that the liver could not produce the volumes of blood the Galenic model required, concluding that there was a fixed and optimal volume of blood circulating in the human body. In 1666, Richard Lower revealed that transfusion could be a life-saving intervention for exsanguination. He bled a dog to the point of death and then performed a carotid artery to jugular vein transfusion from a larger dog - saving the dog's life (21). Later attempts at transfusion demonstrated that the rationale for transfusing blood was unknown, the risks unidentified, and the potential benefits unclear. Attempts were made to perform xenotransfusions from animals to humans to cure madness (22). Despite the efforts to make blood transfusion available, the associated fatalities caused society to abandon the practice.

19th century - the start of transfusions

In 1817, Dr. Henry Leacock noted that blood was species-specific and argued for human-to-human transfusions in conditions such as postpartum hemorrhage or for exsanguinated soldiers suffering from gunshot wounds. The year after, the English obstetrician James Blundell postulated that transfusions could be used to treat postpartum hemorrhage and performed the first human-to-human transfusion, followed by the publication of 10 successful transfusions (23). The first use of the term «shock» to describe the collapse of vital functions in a trauma victim appeared in 1740 by French surgeon Henri Francois Le Dran (24). Later in the 1800s, surgeons frequently stated that death was attributed to shock, but the clinical syndrome was separated entirely from hemorrhage and not understood (25).

20th century - blood groups, cross-matching, blood storage, war experiences,

Well into World War I (WWI), it was believed that «wound shock» was caused by a toxic factor arising from damaged and dying tissue and as a complication of surgery - which led to increased capillary permeability and the escape of plasma, leading to a lower circulating blood volume. Today, we acknowledge that they were right; the release of bradykinin, histamine, and cytokines from trauma and shock adds a distributive shock component to the hemorrhage component. Until WWI, the primary treatment for «wound shock» was strychnine and saline. It was, however, noted that the time factor in treating shock was of great importance. The mortality of injured patients treated within one hour was only 10%, while after 8 hours - mortality was above 75% (26). In 1901, immunologist and Nobel prize winner Karl Landsteiner published his groundbreaking work, identifying blood group-specific agglutinins enabling blood transfusion without endangering the patients' lives (27). However, blood crossmatching in clinical practice was not implemented until later, in 1907, when Ruben Ottenberg performed the first

crossmatched transfusion. In the early 1900s, Lindeman revolutionized the transfusion procedure using syringes and cannulas, replacing surgical procedures pioneered by Carrel, Chile, and others connecting the donor artery and recipient's vein (28, 29, 30). During WWI, «wound shock» treatment revolved around the administration of colloid solutions; the most common was «gum salt» - 6% acacia in 0.19% sodium chloride. However, it was believed that administering whole blood (WB) would be highly effective in treating hemorrhage and shock. Bruce L. Robertson, a Canadian forward surgeon, published an intriguing paper in 1916, arguing for the regular employment and transfusion of WB in war surgery. Although the WB transfusions were uncross-matched, he described a markedly improved survival rate in 36 severely injured patients. He also demonstrated an understanding of the pathophysiology of hemorrhagic shock that is relevant today (31).

Oswald Hope Robertson suggested an improved system for direct blood transfusion in war casualties. In his premise, he understood that there was a need for large-scale blood collection. He tested donors, and only used type O, universal donors that were tested for syphilis. He collected blood in glass bottles with citrate as an anticoagulant, stored it on ice for up to 26 days, and transported it where it was needed. He thus pioneered transfusion at the front line. This approach paved the way for the blood banking systems we see today (32, 33). During and after WWI, the understanding of the pathophysiology of hemorrhagic shock evolved. It was recognized that hemorrhage is the most critical factor in shock and that the blood volume lost defines the degree of shock. Further, the need for oxygen-carrying corpuscles was understood. This supported the conclusion that no other intravenous solutions other than blood could serve the purpose of resuscitation from hemorrhagic shock. In 1927, Blalock presented the modern theory of shock divided into four classes: hematogenic (hypovolemic), neurogenic, vasogenic (anaphylactic and septic), and cardiogenic shock (34). At the entry of WWII, the U.S. position was that freeze-dried plasma (FDP) was sufficient for the

resuscitation of war casualties. However, in the North African campaign, U.K. surgical teams demonstrated better outcomes using WB. As such, the U.S. started a walking blood bank program that lasted until the landings at Normandy. However, the unacceptable outcomes at the landings led U.S. forces to adopt a cold-stored whole blood (CWB) program from U.S. civilian donors (35, 36, 37). During WWII, other colloid solutions were utilized, namely gelatins, pectin, amino acids, oxidized cotton, and dextran.

In 1922, the circulation in bone marrow was described. Due to the known difficulties in attaining rapid access to the circulatory system in patients with hemorrhagic shock, WWII doctors argued that intraosseous (IO) access was a viable alternative (38, 39, 40). Almost 4000 IO procedures were documented during WWII.

After WWII, the US blood program was discontinued. However, in 1950 the Korean War again warranted a system for far-forward resuscitation of hemorrhagic shock. Experience from WWII led to a policy change where only low-titer (Anti-A and -B <256) group O whole blood (LTOWB) was collected to reduce the logistical burden of typing and crossmatching recipients (41). Some 400.000 units of WB were transfused by the end of the war. After the war, it was discovered that severe transfusion reactions sometimes occurred when type-specific whole blood was given after large transfusions of LTOWB. Therefore, it was recommended that after massive transfusion episodes with LTOWB, no type-specific transfusions should occur before at least two weeks elapsed (37).

During the Vietnam War, initially, only LTOWB was shipped. However, blood requirements necessitated the addition of group A and, later, all blood groups. For logistical reasons, only LTOWB was deployed for forward resuscitation. From 1967-1969, 230.323 units of WB were transfused, and 24 hemolytic transfusion reactions were reported. Only one of these reactions was caused by ABO isoagglutinin's in the transfused group O WB unit (42).

During the conflict in Vietnam, Carrico and Shires et al. demonstrated that severe hemorrhage results in a disparate reduction in extracellular fluid volume that could not be accounted for by external loss and that normalization of extracellular fluid volume with isotonic salt solutions improved outcomes (43, 44). The suggestion was to add 1-2L of crystalloids during resuscitation to avoid renal failure. However, this led to an increase in crystalloid use, probably due to the easy logistics of crystalloids compared to blood. As such, a complicating lung-failure syndrome termed «shock lung» or «DaNang lung» became apparent (45). The acute respiratory distress syndrome (ARDS) appeared as an early cause of death after severe hemorrhage. The coagulopathy following serious trauma was frequently discussed during and after the Vietnam War. The empiric conclusion was that this oozing coagulopathy was virtually always reversible, and the suggestion for the treatment was to give fresh WB or plasma sequentially (46, 47).

The 1970s - a shift toward blood component therapy

Following the Vietnam War, infectious disease, blood fractionation, and financial opportunities forced a shift from WB toward blood component therapy (BCT). The most important driver was probably president Nixon´s war on cancer that started in 1971. With chemotherapy came bone marrow suppression and single cytopenias. The blood banks evolved to cater to the isolated problems of low cell numbers. Interestingly, during the transition from WB to BCT, no studies on the efficacy of BCT in treating hemorrhagic shock were published. This transition and the misapplied data from Carrico and Shires et al. probably drove the civilian trauma systems towards the recommendations that early treatment for hemorrhagic shock included external hemorrhage control followed by a rapid infusion of 2000 ml of crystalloids. During the 80s and 90s, it was clear that this philosophy was misapplied, with the overuse of crystalloids often in a ratio >3:1 to estimated blood loss. As a result, patients often received 5-10 L of crystalloids before any blood

product administration (48). In the early 90s, some researchers began to question such treatment algorithms. Bickell et al. demonstrated that restrictive fluid resuscitation with crystalloids in patients suffering from penetrating torso injuries improved survival (49). This led to the adoption of permissive resuscitation (permissive hypotension) strategies for prehospital management of non-compressible hemorrhage. At this time, blood component therapy (BCT) was the mainstay treatment for patients who continued to bleed after 2L of crystalloid therapy.

With the beginning of the conflicts in Southwest Asia following the September 11, 2001 attacks on the U.S. by Al Qaida, the increasing number of injured soldiers in Iraq and Afghanistan sparked a renewed focus on the iatrogenic injury following high volume crystalloid and BCT, as well as the optimal strategy for hemorrhagic shock resuscitation. Again, there was a renewed focus on WB and damage control resuscitation principles in the war theaters (50). The term damage control has its roots in the navy, describing the crew's efforts to keep a leaking ship afloat with temporary salvage techniques so the ship can survive to port. The corresponding medical term highlights rapid temporary hemorrhage control and hemostatic resuscitation efforts to stabilize metabolic disturbances keeping the patient alive until surgical hemorrhage control can be achieved (51). These principles include a permissive hypotension strategy, a balanced transfusion ratio with packed red blood cells (PRBC), plasma, and platelets (PLT), the avoidance of the excessive use of crystalloids, and the principles of damage control surgery (52). Today most civilian hospitals utilize BCT in a balanced ratio in the resuscitation of hemorrhagic shock based on observational data from military experience and the results of the PROPPR trial. However, there is an increased focus on implementing LTOWB for pre- and in-hospital resuscitation of hemorrhagic shock (53, 54, 55). At the same time, economic issues and safety concerns promote strategies for maximum utilization of available blood and more restrictive guidelines (56).

After year 2000 - have we come full circle?

Modern damage control resuscitation (DCR) represents a bundle of care principles first described by Holcomb in 2007 aimed at improving outcomes in patients suffering from traumatic hemorrhage and hemorrhagic shock. DCR principles emphasize early compressible hemorrhage control, hypotensive resuscitation, rapid evacuation and surgical control of bleeding, avoidance of hemodilution from overuse of crystalloids and colloids, prevention of acidosis and hypothermia, and hemostatic resuscitation with blood or blood components (52). The modern principles of hemostatic resuscitation represent a paradigm shift in the treatment of hemorrhagic shock. However, the core principles are, in many ways, a reintroduction of earlier methods and interventions.

1.3. Hemorrhagic shock - definition and pathophysiology

Definition of shock

The classical definition of shock is that tissue oxygen delivery to tissues is insufficient to meet metabolic demands (57). In this state, oxygen consumption is delivery-dependent, and reduced delivery of oxygen causes a metabolic shift towards anaerobic metabolism (glycolysis) (58).

Oxygen deficit and oxygen debt

The oxygen delivery to the tissues (DO_2) can be derived from Fick´s principle, where key determinants are cardiac output, hemoglobin concentration, and oxygen saturation (59).

To understand the concept of oxygen debt and shock, one must look at the biphasic relationship between oxygen delivery (DO_2) and consumption (VO_2) (Figure 1.).

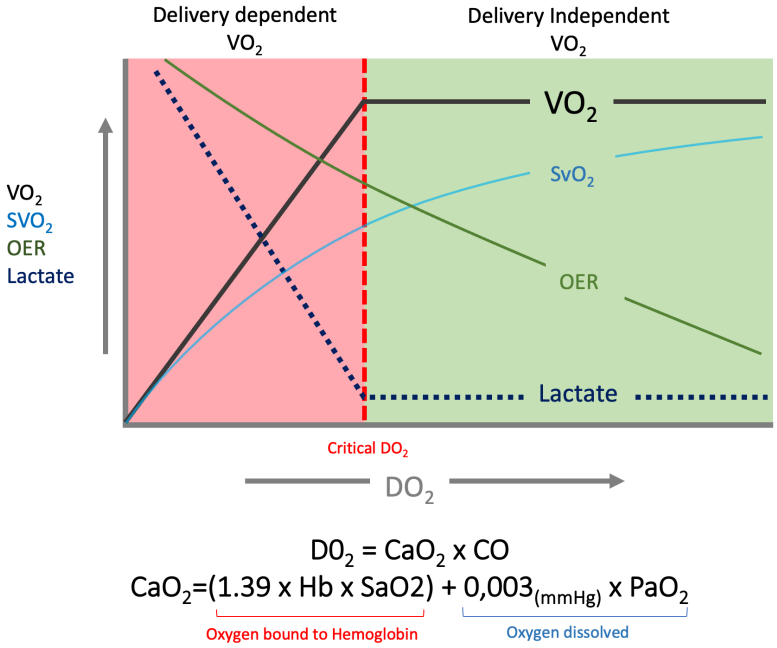

Figure 1. The biphasic relationship between DO_2 and VO_2

In a normal resting state, oxygen consumption (VO_2) is independent of oxygen delivery (DO_2). DO_2 can vary widely without a drop in VO_2 since oxygen extraction (OER) can increase to meet tissue metabolic demand (VO_2) (green area). However, if severe hemorrhage causes a drop in DO_2 beyond tissue VO_2 (critical DO_2), VO_2 becomes directly dependent on DO_2. This inflection point (represented by the red vertical line) represents the transition from mass aerobic metabolism to mass anaerobic metabolism, an ischemic state where an oxygen deficit exists. In the delivery-dependent state, the oxygen extraction ratio (OER) is increased, as reflected in reduced central venous oxygen levels (SVO_2).

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The duration and magnitude of shock can be labeled as the «shock dose» and will be a measure of the body's oxygen debt. The greater the shock dose (duration/ magnitude), the greater the final tissue damage and organ dysfunction after reperfusion. However, the tolerance to oxygen debt varies among different tissues.

The pathophysiological consequences of oxygen debt have been described in several studies and are linked to morbidity and mortality and the development of multiorgan failure(60, 61, 62).

Pathophysiology of hemorrhagic shock

As shock persists, cellular function deteriorates. The anaerobic metabolism leads to an accumulation of lactic acid, inorganic compounds, and free radicals (58). In this process, the release of mitochondrial DNA and formyl peptides known as damage-associated molecular patterns (DAMPs or alarmins) incites a systemic inflammatory response (63). Ultimately, critically impaired ATP supplies cause cellular homeostasis to fail, leading to cell death due to membrane rupture, apoptosis, or necroptosis. Hemorrhage is followed by hypovolemia, capillary vasoconstriction, and thrombosis, which causes organ hypoperfusion. The net result is organ dysfunction and, ultimately, organ failure that leads to multi-organ dysfunction. At the mitochondrial level, the oxygen deficit restricts oxygen from serving as the terminal electron acceptor (oxidant) in the electron transport chain, leading to a significant decrease in ATP production. The increased mitochondrial electron burden leads to a destabilization of the mitochondrial membrane and the opening of mitochondrial pores. This permits the leakage of ions, metabolites, and macromolecules, leading to mitochondrial swelling and membrane depolarization. Cytochrome c is also released, leading to the activation of apoptosis activating factor 1 (Apaf1) and the formation of the apoptosome (64). The mitochondrial damage may be accelerated by proteolytic enzymes and reactive oxygen species (58). In addition, highly reactive oxygen species are formed due to the breakdown

of the catalase and glutathione peroxidase system (65). The ongoing production of these oxidants may cause irreversible cellular damage in the form of lipid peroxidation, protein nitrosylation, and DNA damage (66). Paradoxically, the production of these oxidants is exacerbated by reperfusion, as more oxygen is available to react with the free electrons. Hence, the greater the ischemic burden, the greater the tissue injury will be following reperfusion.

Although the described dynamics of impaired oxygen delivery cause alterations at the cellular levels that lead to organ dysfunction and affect the endothelial system, coagulation system, and immune system, it is also worth noting that severe hemorrhage may cause rapid exsanguination with subsequent pulselessness that may cause a rapid cerebral and myocardial hypoperfusion leading to anoxic brain injury, heart failure, or fatal arrhythmia within minutes.

Adrenergic response to shock

Hemorrhagic shock leads to the activation of the sympathetic nervous system. This process is characterized by catecholamine release due to pain and tissue injury that induces cardiovascular compensatory mechanisms, including increased heart rate, relaxation of pulmonary smooth muscle, and the activation of energy stores in the liver. The peripheral compensatory vasoconstriction exacerbates tissue oxygen deficit due to reduced blood flow. Adrenergic activation also stimulates the Na^+-K^+-ATPase resulting in increased lactate production (67). Although some tissues may utilize lactate as fuel, increased lactate levels lead to acidosis. Recent publications demonstrate that sustained high catecholamine levels directly impair endothelial function through increased permeability and glycocalyx shedding (68, 69, 70).

Clinical relevance of oxygen debt

An often overlooked significant factor in the resuscitation of hemorrhagic shock is the importance of timely repayment of critical portions of the debt as soon as possible (57). Compared to other physiological debts, such as sleep, it is impossible to incur a significant debt and suffer no consequences. As such, resuscitative efforts that halt the accumulation of oxygen deficit by returning to a DO_2-independent VO_2- state are essential but usually insufficient to achieve homeostasis. Critical energetic cellular systems such as the phosphagen and glycogen-lactic systems may be significantly depleted during shock (71).

Identifying, quantifying, and monitoring the oxygen debt are major challenges in the prehospital environment. Currently, no tools allow providers to assess the oxygen debt and when it has been repaid. Further, it is unknown how much debt can be tolerated over what period other than to speculate that there probably is a significant inter-individual difference (72). Currently, the most physiological approach may be initiating resuscitation early and rapidly normalizing lactate and the body's oxygen extraction ratio to maximize chances of timely oxygen debt repayment and reversal of hemorrhagic shock (73)(Fig.2).

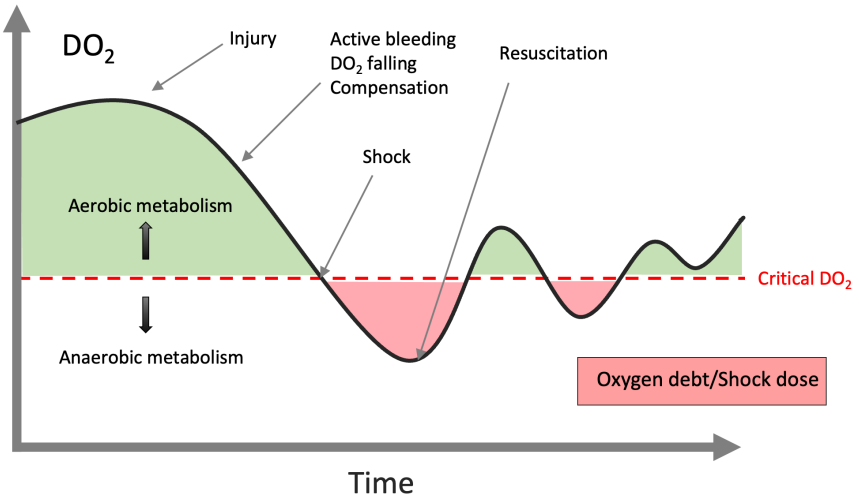

Fig. 2 Conceptual schematic overview of oxygen debt accumulation in non-compressible hemorrhage

Following hemorrhage, failure to control active bleeding inevitably leads to reduced DO_2 to the tissues. When the compensatory mechanisms fail to sustain adequate DO_2, the organism enters a state of shock at the critical DO_2 level.

The overall aim should be to resuscitate to reduce the accumulation of oxygen debt.

1.4. «Blood failure»

The classical understanding of coagulopathy following hemorrhage

There has been a significant focus on improving early mortality in patients suffering from major hemorrhage and hemorrhagic shock. One of the main challenges recognized since the early 19th century is the development of early hemostatic dysfunctions, today recognized as coagulopathies (74, 75, 76). The

development of early coagulopathies after significant bleeding has predominantly been studied in the trauma population; however, a common problem is the critical care of patients suffering from major hemorrhage unrelated to trauma. Despite the poor evidence that bleeding after surgery, gastrointestinal and obstetric hemorrhage are associated with hemostatic changes similar to the patients suffering from hemorrhage after trauma, treatment protocols and therapeutic aims are the same (77).

Traditionally the development of coagulopathy has been attributed to the dilution of coagulation factors, acidosis, and hypothermia following major bleeding, termed the «lethal triad.» Hemorrhage leads to loss of hydrostatic pressure, followed by a fluid shift from the extravascular space into the circulation. This mechanism has been described as auto-resuscitation as a response to hypovolemia. On the other hand, the resulting dilution of remaining coagulation factors has detrimental effects on coagulation (78). The administration of crystalloids may further exacerbate this effect. Hypothermia is a known complication in major trauma and hemorrhagic shock, especially in the prehospital setting. Decreased oxygen delivery to tissues reduces ATP production and lower heat production. Heat loss to the environment, immobility, anesthetic drugs and administration of cold fluids inevitably aggravate hypothermia in these patients. It has been shown that temperature affects the performance of the coagulation system. The optimal temperature for coagulation is 37ºC, and deviation causes a reduction in coagulation performance (79). Further, hemorrhage leads to the accumulation of oxygen debt. The resulting anaerobic metabolism and increased lactate levels affect acid-base homeostasis. The optimum pH for activation of the coagulation cascade is slightly above the normal physiologic levels. As such, it has been shown that FVII activity is reduced by 90% at pH 7,0 (80).

In certain hemorrhages, there is a significant effect of the consumption of coagulation factors. The rapid consumption of coagulation factors can be observed

in the setting of blunt trauma mechanisms if large areas of damaged tissue are exposed to the circulating system. Similar effects are seen in postpartum hemorrhage. This is particularly evident in fibrinogen levels, which tend to decline rapidly early in trauma (81, 82).

Modern understanding of coagulopathy and endotheliopathy following hemorrhage

Recent data has demonstrated that coagulopathy following traumatic bleeding cannot be adequately explained by classical mechanisms alone. In trauma patients, it has been recognized that disruption of hemostatic equilibrium begins at the moment of traumatic impact. Brohi et al. demonstrated that about a quarter of the patients had developed coagulopathy at admission to the hospital, even within 20 minutes after injury. Further, they found that the presence of coagulopathy predicted the incidence of multi-organ dysfunction and intensive care utilization. The presence of early coagulopathy has been associated with a four-fold increase in mortality. Similar results were presented in another contemporary study (74, 75). As a result, the early onset of coagulopathy in the trauma population is termed acute traumatic coagulopathy (ATC). Subsequent medical interventions may affect and exacerbate ATC by several mechanisms leading to the complex syndrome termed trauma-induced coagulopathy (TIC).

Due to these findings, researchers have focused on pro- and anti-hemostatic mechanisms that precede and aggravate the effects of the classical mechanisms.

Systemic anticoagulation - The protein C pathway

One prevailing theory is that ATC development is driven by hypo-perfusion leading to an increase in thrombomodulin which diverts thrombin from fibrin generation towards the activation of protein C. Activated protein C (aPC) is known to cleave FVa and FVIIIa. As such, the theory postulates that this results in

systemic anticoagulation because of the resultant inhibition of thrombin generation. Secondly, aPC has been proposed as an inhibitor of plasminogen activator inhibitor-1 (PAI-1). This would then lead to an increase in plasmin generation and, subsequently, an acceleration of fibrinolysis (82, 83). However, there are several issues related to the role of aPC in systemic anticoagulation. First, the levels of aPC observed in ATC are far from the concentration that can cleave platelet and plasma FVa sufficiently to cause systemic anticoagulation (84). Further, aPC binds PAI-1 in a 1:1 fashion. Since there are about ten times higher levels of PAI-1 compared to the amount of protein C, it seems unlikely that this would cause a significant effect on fibrinolysis (85, 86, 87). Also, a systematic review found no reports on the protein C-mediated neutralization of PAI-1 (88). Hence, although activated protein C has both anticoagulant and pro-fibrinolytic effects in normal hemostasis at the site of injury, it is unlikely that the protein C pathway is the culprit in the systemic development of ATC (89).

Fibrinogen depletion

The rapid decline in fibrinogen levels after trauma and obstetric bleeding has been well documented. In obstetric bleeding, fibrinogen depletion has been identified as an early predictor of severe postpartum bleeding. The mechanism of fibrinogen loss in trauma and postpartum hemorrhage continues to be the subject of debate and ongoing research. The leading theory is linked to the exposure of large areas of damaged tissue to circulating blood, causing significant consumption. Iatrogenic dilution also seems to play a role (81, 82, 90). Fibrinogen supplementation with cryoprecipitate (UK or U.S.) or fibrinogen concentrate (Europe) has traditionally been considered a second-line therapy in the delayed treatment of hemostatic dysfunction in trauma patients. In contrast, early fibrinogen supplementation has been commonplace in postpartum hemorrhage and cardiac surgery. The potential benefit of early fibrinogen supplementation in trauma is the subject of a large randomized controlled trial - CRYOSTAT-2 (91). Currently, the relative

contribution of hypofibrinogenemia to the development of ATC and the critical clinical threshold levels is still questioned (81).

Reduction in red cell mass

Circulating red cells significantly affect primary hemostasis as they tend to flow through the center of the artery or arteriole. In normal hematocrit levels, this causes the plasma and platelets to be marginated towards the vascular wall. In the event of vascular injury, this phenomenon facilitates early platelet and coagulation factor interaction with the damaged vessel wall. However, this effect is disrupted once the hematocrit falls below about 30% (92, 93). As such, it has been shown that there is an inverse relationship between hematocrit and *in vitro* bleeding time (94).

Excessive fibrinolysis

The clinical importance of fibrinolysis has been demonstrated by the CRASH-2 trial showing a survival benefit when blocking this pathway with tranexamic acid during hemorrhage (95). Excessive fibrinolysis is caused by local tissue response to hypo-perfusion, leading to the release of tissue plasminogen activator (tPA). The release of tPA is modulated by circulating epinephrine, vasopressin, and thrombin signaling. Circulating tPA catalyzes the conversion of plasminogen to plasmin, causing fibrinolysis and the dissolving of blood clots. In this setting, tPA will improve local perfusion in damaged tissue areas, yet in severe injury, it may have systemic adverse effects (96). This is the most critical factor in the development of ATC as it is consistent with current knowledge and the timing of observed effects. The drop in middle arterial pressure in hemorrhage stimulates tPA release within 20-30 minutes, which causes plasmin activation and initiation of fibrinolysis. The plasmin-antiplasmin complex (PAP) can be measured and is a sensitive indicator for the activation of fibrinolysis, and the levels are significantly increased in most severely injured trauma patients (97). Again, the timing of the development of

fibrinolysis following these mechanisms is consistent with the observed improved outcomes following early (<1h) administration of tranexamic acid (95).

Platelet dysfunction

Functional platelets are vital components in the maintenance of vascular integrity after injury. Platelets activate, accumulate, aggregate, and provide a scaffold for thrombin and fibrin mesh generation to provide a platelet plug that participates in mechanical hemostasis. Subsequent clot retraction facilitates the repair of damaged vascular tissue edges. Platelet dysfunction is observed in trauma patients, even in the presence of a normal platelet count and regular standard clotting panels. It has profound implications for mortality (98, 99, 100). In a sub-study of the PROPPR trial, patients who received platelets early had better outcomes (101). However, the mechanisms underlying trauma-associated PLT dysfunction are an area of continued research. Animal studies have suggested that PLT dysfunction is caused by changes in intracellular cyclic AMP and bioenergetic failure (102). Other factors, such as oxidative stress during hemorrhagic shock and high intracellular calcium levels, may play a role (103).

Interestingly, research has also shown that a low Glasgow coma scale is an independent predictor of platelet dysfunction in trauma patients, highlighting the potential link between TBI and PLT dysfunction (98). As such, the impact of dysfunctional platelets in the early course of trauma is an area of research. Unfortunately, early evaluation of platelet function has proved difficult, as standard available assays like PT and INR neglect platelet function. Functional tests like platelet aggregation and newer viscoelastic testing with platelet mapping may provide further insight into this issue.

Endotheliopathy

Coagulopathy develops in parallel with a dysfunction in the endothelial system. The microcirculation with its endothelial lining is estimated to represent an area above 3000m^2. It is responsible for critical regulated processes such as the delivery

of oxygen, hormones, nutrients, and waste removal (104). It may be considered the body's largest integrated organ system. This system is highly affected by hemorrhage, hypo-perfusion, and resulting reperfusion injury (105). Endotheliopathy following injury can be characterized by dysfunctional hemostasis, increased paracellular permeability, and inflammation. It essentially corresponds to what clinicians called «wound shock» in WWI. The degree of endothelial damage is largely modulated by the scope of direct damage, the degree, and duration of hypo-perfusion, and is affected by the accompanied sympathoadrenal activation. The resulting endothelial activation leads to an overwhelming release of tPA and hyperfibrinolysis. In addition, hypo-perfusion has been shown to result in the shedding of the endothelial lining - the glycocalyx, releasing antithrombotic syndecans into the bloodstream, a concept known as auto heparinization. The shedding of the glycocalyx is correlated with circulating catecholamines and mortality (69, 106, 107, 108).

Clinical evaluation of coagulopathy

In addition to standard tests such as activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalized ratio (INR), several other tests are available. From a clinical perspective, point-of-care testing has been developed for the early evaluation and recognition of hemostatic dysfunction. The viscoelastic tests of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are global tests of hemostasis performed on whole blood (109). These tests may be performed bedside to rapidly assess the kinetics of clot formation, strength, and dissolution. The thromboelastogram provides information on the time to initiation of fibrin clot formation, speed of initial clot formation, rate of fibrin cross-linking, the clot's maximum strength, and the clot's degradation. From the thromboelastogram, targeted treatment may be suggested based on the identified pathologies. In addition, impedance aggregometry testing may be utilized to identify platelet dysfunction (110). Although viscoelastic tests

are promising, they suffer from clinically significant shortcomings, such as the dependence on clinical judgment and interpretation (111). In addition, the impact of viscoelastic testing in the early phases of non-compressible hemorrhagic shock is limited due to the time delay in obtaining the results.

In summary, it is evident that a deeper understanding of the development of ATC and how to treat it is essential to reduce morbidity and mortality after trauma and hemorrhagic shock. Researchers agree on the complexity of ATC and that its underlying causes need to be better understood. Moreover, current diagnostic criteria such as PT, INR, and viscoelastic assays are insufficient to get complete oversight on the complex development of coagulopathy after hemorrhagic shock. Thus, there is a lack of diagnostic tools that can provide guidance among a myriad of treatment options. Hence, the multivariate nature of the conditions needs to be addressed from their root causes rather than attempting to correct deviations in inconclusive tests (89). The development of the different pathophysiological components is driven and exacerbated by shock and the accumulation of oxygen debt. While the linkage between shock and traditional organ failure has long been recognized, both the endothelium and blood are very sensitive to oxygen debt. They can be regarded as an integrated organ system at risk of failing, impacting all other organ systems. Hence, the combination of oxygen debt-driven endotheliopathy and coagulopathy might be considered collectively as «blood failure» due to the highly connected networks between the systems and the subsequent failure in hemostasis during hemorrhagic shock (112, 113)(Fig.3). In the prehospital setting, the consequence would be to direct efforts towards mitigation of oxygen debt accumulation and oxygen debt repayment to reduce the severity and duration of the shock.

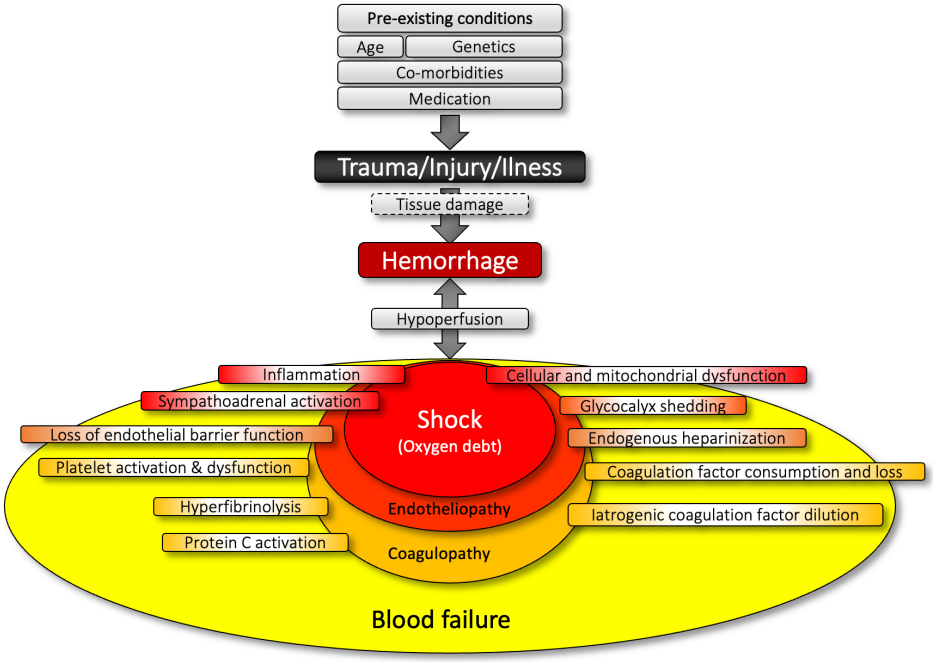

Fig. 3 Framework for the initiation and evolution of blood failure

The figure outlines the framework and the individual components in the development of blood failure.

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1.5. Remote damage control resuscitation

The distinct field of RDCR

Although the implementation of modern RDCR principles may represent a paradigm shift in the prehospital care of patients suffering from hemorrhagic shock, the strategy for providing basic point-of-care interventions, controlling hemorrhage, and rapid transport to medical treatment facilities has been practiced

for centuries. However, to facilitate a successful outcome, the patient must survive transport and possess sufficient biological reserves to endure advanced treatment in the hospital. Therefore, RDCR principles have been described as the implementation of DCR strategies in the prehospital setting (114). DCR principles include compressible hemorrhage control, hypotensive resuscitation, avoidance of the overuse of clear fluids, prevention and correction of acidosis and hypocalcemia, hemostatic resuscitation (early use of a balanced transfusion with red cells, plasma, and platelets), and moving as fast as possible to damage control surgery for definite hemorrhage control (52). The RDCR principles reflect the same goals but take into account the differences in the immediate goals, available resources, and optimal management strategies between prehospital and in-hospital care.

With the implementation of the RDCR principles, it is essential to distinguish between patients suffering from hemorrhagic shock from non-compressible hemorrhage and patients who can achieve hemorrhage control early. For instance, the concept of hypotensive resuscitation may be detrimental to the latter in the case of delayed evacuation. Hypotensive resuscitation is a controversial practice which will be discussed below.

Management of hemorrhagic shock - RDCR vs. DCR

Although some trauma systems employ experienced prehospital physician-led teams to the point of injury, most prehospital DCR providers are typically first responders, EMS personnel or paramedics in the civilian setting, and combat medics, paramedics, or hospital corpsmen in the military environment. As such, these small prehospital teams may lack experience with patients in severe hemorrhagic shock compared to the highly resourced, specialized in-house trauma teams. There is also a distinct difference in the availability of diagnostic tools such as radiology, ultrasonography, advanced monitoring, and laboratory assays.

Further, the limited availability of therapeutic options in the prehospital environment, such as available blood and blood products, hemostatic adjuncts, and surgical capabilities, highlight the logistical problems of RDCR. Moreover, prehospital providers may have different short-term goals due to the nature of the situation on the scene. Extrication challenges, immediate threats, weather conditions, noise, darkness, confined areas, triage, and evacuation logistics may influence the individual patient's resuscitation efforts. The nature of prehospital care and its challenges dictates that the providers carefully conserve resources and prioritize time-critical interventions to improve outcomes.

For instance, the threshold for advanced airway management differs in the prehospital phase, as the risk of intubation and positive pressure ventilation are increased due to the inability to monitor and volume load the patient (115). Another significant hurdle in the early care of patients suffering from hemorrhagic shock is the timely obtainment of vascular access. Prehospital intravenous (IV) access may be complicated in some patient groups, especially in bleeding patients (116, 117). Data show that prehospital IV access is associated with longer on-scene times (118). The rapid obtainment of vascular access, for example, via an intraosseous route, is vital to facilitate early hemostatic resuscitation. These aspects underscore the differences between RDCR and DCR and the need to direct future research efforts to the applications and outcomes of prehospital and in-hospital interventions separately.

RDCR Principles - Compressible hemorrhage

One of the core principles of RDCR is to stop or reduce ongoing bleeding as soon as possible to minimize the consequences of hypoperfusion and oxygen debt and to augment the hemostatic response. This principle has been highlighted both in civilian and military trauma care. In recent years, the traditional ABC approach in Advanced Trauma Life Support (ATLS) has been questioned, noting that massive,

life-threatening bleeding should be addressed before airway management (119). In the military framework, this concept is implemented in the MARCH algorithm in the Tactical Combat Casualty Care (TCCC) guidelines (120). Ultimately, early hemorrhage control can be achieved by detecting the source of bleeding, applying direct or proximal pressure, and elevating the bleeding site. However, hemostatic adjuncts may be necessary to achieve a beneficial outcome. These adjuncts may be divided into «mechanical» adjuncts, which refer to devices that stop or reduce hemorrhage, or «injectable» hemostatic adjuncts, which refer to plasma derivatives or substances that affect the coagulation system and provide hemostatic effects. A summary of available hemostatic adjuncts is presented in table 1.

Table 1. Hemostatic adjuncts in RDCR

Category	Adjunct	Mechanism of action
Mechanical	Gauze	External compression or wound packing directly at the site of injury. Often used in combination with compressible dressings or clamps.
	Topical hemostatic agents	Gauze or dressings impregnated with substances with hemostatic properties. (Chitosan, kaolin)
	Pelvic binder	Reduction and stabilization of fractures in the pelvic ring, reduction of pelvic volume - decrease potential space for blood loss.
	Extremity tourniquet	Proximal external compression of arterial blood supply to extremity
	Junctional tourniquet	Proximal compression of arterial supply in axilla or groin in injuries not amenable to extremity tourniquets.
	Abdominal aortic tourniquet	Proximal compression of abdominal aorta for pelvic or junctional injuries not amenable by junctional tourniquets
	External soft tissue clamps	Retractable external clamps that reduce and contract soft tissue lacerations. Often used in combination with gauze.
	Expandable hemostatic agents	Percutaneous injection of expandable substances for temporary control of internal hemorrhage
	REBOA[1]	Endovascular total or partial balloon occlusion of aorta for pelvic or abdominal hemorrhage.
Injectable	Tranexamic acid	Lysine analog that inhibits the activation of plasminogen to plasmin - antifibrinolytic
	Prothrombin complex concentrate	Plasma-derived agent made up of coagulation factors II, IX and X. Some agents also contain VII, protein C and antithrombin
	Recombinant Factor VIIa	Activated form of FVII
	Cryoprecipitate	Plasma derived preparation rich in fibrinogen and coagulation factors VIII, XIII and vWF
	Fibrinogen concentrate	Lyophilized fibrinogen powder

Table 1. Outline of hemostatic adjuncts available for RDCR

The table shows the mechanical and injectable adjuncts in current use. ([1]REBOA: Resuscitative Endovascular Balloon Occlusion of the Aorta)

RDCR Principles - Hypotensive resuscitation

Hypotensive resuscitation has been a central yet controversial concept in RDCR. Several other terms describing the same context, such as permissive hypotension, delayed resuscitation, permissive resuscitation, and hypo-resuscitation, have been presented in the literature. A part of the original justification of the concept of hypotensive resuscitation was to avoid the transient increase in blood pressure following aggressive clear fluid administration in patients suffering from non-compressible hemorrhage. The following increase in blood pressure might disrupt the endogenous formed clotting processes and increase a bleeding tendency (121).

Data from civilian trauma systems has demonstrated that a restrictive clear fluid strategy reduced mortality in penetrating torso trauma (49, 122). These studies were conducted in settings with short evacuation times. In contrast to these studies, two non-randomized controlled trials examining patients with either penetrating or blunt trauma injuries alone found no significant differences in survival (123, 124). Targeting resuscitation efforts toward a palpable radial pulse and/or an appropriate level of mentation has been a typical strategy in civilian and military trauma systems. Hence, a restrictive fluid administration regimen until definitive hemorrhage control requires accepting a period of suboptimal end-organ perfusion. Conversely, a restrictive clear fluid resuscitation policy may reduce the incidence of secondary complications of aggressive clear fluid therapy, such as abdominal compartment syndrome, coagulopathy, and acute respiratory distress syndrome (122, 125, 126). The strategy may be described as a «necessary evil» - sacrificing perfusion to reduce bleeding. However, the evidence is sparse. First, in the event of concomitant traumatic brain injury, permissive hypotension may be contraindicated. Second, in civilian EMS systems where elderly patients are heavily represented, with comorbidities and various medications, there is limited data on how the strategy will affect outcomes. Last and most important, as many EMS services are now implementing hemostatic resuscitation with blood products,

it is problematic to extrapolate data from the excessive use of crystalloids and hypotensive resuscitation to the use of blood and blood products. As such, reviewing the strategy, one must consider the type of injury (penetrating vs. blunt), non-traumatic hemorrhage, the likelihood of intracranial injury, resuscitation fluid available, and the proximity to a medical treatment facility and definite hemorrhage control.

RDCR Principles - Correction of acidosis, hypothermia, and hypocalcemia

The development of acidosis resulting from the production of lactate, acidic metabolites, and unmeasured anions during hypo-perfusion and shock contributes to trauma mortality. Data show that the degree of acidosis upon arrival to the emergency department correlates with the degree of coagulopathy and mortality (127, 128). While emerging acidosis has some adaptive aspects, as it aids oxygen extraction at the cellular level, it has multiple adverse effects, including worsening coagulopathy, increased compensatory respiratory minute volume, and decreased responsiveness to catecholamines. Aggressive infusions of saline may contribute to developing acidosis since normal saline has a pH of 5,5. In addition, the high chloride fraction may contribute to hyperchloremic acidosis.

Hypothermia aggravates the complications of shock. Patients suffering from hemorrhagic shock lose their ability to generate heat and sustain a normal core temperature. A recent study showed that > 70% of trauma victims were hypothermic on the arrival of EMS providers (129). In RDCR, efforts should focus on aggressive hypothermia prevention, including passive and active rewarming utilizing blood-warming devices and heated blankets.

RDCR Principles - Hemostatic resuscitation

The final principle of RDCR is early hemostatic resuscitation, with the ultimate goal of restoring or sustaining adequate tissue perfusion and oxygen delivery while preserving effective coagulation and clotting in non-compressible hemorrhage. Most guidelines address the importance of the time factor - to initiate resuscitation as early as possible and to reduce the time elapsed between injury and bleeding control to a minimum. Shackelford et al. found that only transfusions commenced within 15 minutes of medical evacuation (between 30-40 minutes from injury) were associated with reduced 24-hour mortality in combat casualties (130). The physiologic rationale would be to prevent or minimize the impact of hemorrhagic shock and its consequences before it is allowed to evolve. However, in contrast to hospital-based DCR, prehospital blood transfusions for hemorrhagic shock are still a subject for debate, at least in the civilian setting. A systematic review found that using PRBC and plasma prehospital reduced the odds of long-term mortality. Still, the authors were careful in concluding a potential survival benefit of prehospital BCT (131). One RCT (RePHILL) found no difference in survival comparing prehospital plasma and PRBC transfusions versus crystalloid infusions in severely injured trauma victims (132). However, the time to intervention in this study was above 50 minutes, questioning the potential effect of any of the interventions. Similar results were presented in the COMBAT trial (133). In this trial, prehospital time was extremely short, averaging 20 minutes. Again, the short timespan questions the potential futility of the intervention, notably when only a minority of patients received an intervention of two units of plasma before hospital arrival. On the other hand, the RCT by Sperry et al. (PAMPer) found that using plasma improved survival compared to crystalloids in a prehospital setting (134). Post-hoc analyses of PAMPer found that patients receiving both plasma and PRBC had the best outcomes (135). Furthermore, pooled data from PAMPer and COMBAT demonstrated that pre-hospital plasma transfusion was associated with a survival benefit when the pre-hospital times were more than 20 minutes (136). At last,

Braverman et al. conducted a retrospective study that compared no prehospital transfusion to LTOWB transfusion for patients in hemorrhagic shock and found that patients who received LTOWB transfusion prehospital had a more significant improvement in shock index (heart rate divided by systolic blood pressure) and a reduction in early mortality (137).

Either way, the overall goal to provide hemostatic resuscitation early is standard in most systems. Internationally, there are three leading in-hospital approaches to hemostatic resuscitation (138). The European guidelines recommend goal-directed (GD) therapy based on viscoelastic testing (VET) and laboratory assays (139). The predominant rationale for this method is that this therapy addresses the individual patients' derangements in TIC. As such, goal-directed BCT can be considered an alternative that provides an individualized approach to the bleeding patient (140, 141). Although GD therapy may provide a physiological and targeted approach that may limit the waste of blood products, the protocols are not straightforward, and the accuracy may be operator dependent. Further, relying on VET may be problematic as the results are not time sensitive. In addition, randomized data supporting VET-guided therapy are limited. A single-center study demonstrated a survival benefit, but a more extensive multi-center study did not (142, 143). Lastly, this therapy is not available for prehospital settings and RDCR.

The second approach is to apply hemostatic resuscitation with BCT in a fixed ratio. This approach relies less on diagnostics than GD therapy and represents a more straightforward strategy with simple protocols and uniform dosing. The justification of fixed-rate BCT for bleeding patients is based on the mechanistic rationale of providing a balanced 1:1:1 resuscitation with PRBC, plasma, and PLT in a ratio that is the closest approximation to WB to improve survival (9). The PROPPR trial investigated the efficacy of a fixed 1:1:1 ratio of plasma, PLT, and PRBC compared to a 1:1:2 ratio and found no differences in 24h and 30-day mortality between the two groups (55). However, in the 1:1:1 group,

fewer patients died from exsanguination within 24 hours, and more patients achieved hemostasis. The PROPPR trial received criticism for confounding factors and inconsistencies, mainly because patients never received an actual 1:1:1 ratio during resuscitation. For instance, plasma was given well after (> 6 hours) of initial resuscitation. This «catch-up» phenomenon points to a common problem in fixed ratio BCT resuscitation strategies - all components are not necessarily available at all time points. As such, although providers may «end up» with a balanced 1:1:1 ratio, it doesn't mean that the patient has received balanced BCT at all phases. Regarding PLT therapy, as stated above, patients who receive PLT early have better survival, highlighting the need to consider PLT-containing products in a prehospital setting (101). Further research is needed to determine the mortality benefit of 1:1:1 vs. 1:1:2 therapy. In prehospital RDCR, fixed ratio BCT is currently a logistical challenge. PRBC may be stored and deployed in RDCR, but fresh frozen plasma and platelets are logistically challenging to provide prehospital due to the infrastructure necessary to prepare and store these products in the field. For instance, room-temperature stored platelets are stored and agitated in a room-temperature incubator. However - lyophilized and liquid plasma and cold-stored platelets may be an option prehospital.

The third conceptual approach is to provide hemostatic resuscitation with WB. The supporting rationale for this strategy has been to provide the patient with a product similar to what is lost. Further, the simplistic protocols, uniform dosing, and potential benefit of avoiding the hemodilutional effects of BCT have been highlighted. Additionally, the WB approach provides the patient with a properly balanced transfusion in all resuscitation phases, avoiding the «catch-up» phenomenon (discussed in detail below). On the other hand, few RCTs support its use, and there are concerns about the logistics, short shelf life, safety, and potential waste. The potential mortality benefit of WB has been investigated in a recent prospective multi-center observational study. Compared to BCT, WB was associated with a 48% reduction in mortality in trauma patients (144). A similar

prospective observational study demonstrated that using LTOWB increased the odds of 24-hour survival by 23% (OR 0.81) (145). For prehospital interventions, the aforementioned retrospective study demonstrated an improved shock index and a reduction in early mortality (137). In the non-trauma patients, there is a paucity of data describing its use, highlighting the need for more outcome data in this population (146). Randomized trials comparing WB to BCT have been proposed and are beginning to enroll in both the U.S. and Europe. An outline of future studies is outlined below.

1.6. Blood products for prehospital hemostatic resuscitation

The availability of blood products in the prehospital arena depends on several factors, including local policies, storage facilities, logistical constraints, and availability and proximity of blood banks and blood donors. The financial burden of a prehospital blood transfusion program is also relevant in the cost-benefit analysis. A European survey of prehospital blood transfusion found marked dissimilarities in practice between the countries. Overall, 48% of the services had access to PRBC, 22% fresh plasma, and 14% FDP. Fifty-five % of the services stated that prehospital blood transfusions are beneficial and, in some individual cases, life-saving (147). Table 2. presents the blood products available in RDCR.

Product	Storage	Shelf life
Whole blood (WB)	2-6ºC	21 days (CPD,CP2D)[1] 35 days (CPDA-1)[2]
Warm fresh whole blood	Stored in donor or after donation as WB	In donor or as WB (above)
Red blood cells	2-6ºC	Up to 42 days (35 days in Norway)
Lyophilized plasma	2-25ºC	Up to 2 years
Liquid plasma	1-6ºC	26 days (CPD) 40 days (CPDA-1)
Thawed plasma	1-6ºC	5 days
Cold stored platelets	2-6ºC	14 days

Table 2. Outline of the blood products available in RDCR

The table shows the storage conditions and shelf life of blood and blood products in RDCR. Room temperature stored platelets is not available for RDCR due to a 5-7 day shelf life and the need for agitation and an incubator. ([1]CPD: Citrate-Phosphate-Dextrose [2]Citrate-Phosphate-Dextrose-Adenine)

Red cells

Red blood cells are critical in oxygen delivery to the tissues, critical enzymatic processes, and buffering the blood (148). As mentioned earlier, red cells provide the bulk of the clot mass and ensure the margination of platelets to the vessel wall in the bloodstream, ensuring platelet interaction with the damaged vessel (93). Red blood cells have historically been among the first products administered in resuscitation due to their role in oxygen delivery and easy administration in blood banking practice. Their shelf life of 42 days is also beneficial in the avoidance of unnecessary waste. However, multiple studies have addressed the red cell storage lesion that causes altered membrane shape, reduced oxygen-carrying capacity, and membrane integrity. Observational data suggests that old PRBC cause harm, but no RCT has found evidence of such(149, 150). Although PRBC remains an integral part of DCR together with plasma and platelets, transfusion of old red

cells to patients in hemorrhagic shock may result in a greater likelihood of poor outcomes (151, 152, 153, 154).

Plasma

The transfusion of plasma in hemostatic resuscitation should be evident as plasma contains all the necessary enzymes and substrates to produce a clot and supports vascular integrity during hypo-perfusion. In addition, plasma has a favorable colloid-osmotic profile that restores and sustains intravascular volume in shock. Fresh frozen plasma is the most common plasma product available.

FFP is separated from whole blood by centrifugation and stored at -18ºC or colder with a shelf life of up to 3 years, dependent on storage temperature. The thawing process is originally performed by gentle agitation in a 30-37ºC water bath or warming device over 30-40 minutes. Although newer portable rapid thawing devices may allow FFP to be thawed in 5- 15 minutes, the option is still cumbersome in austere environments and in time-critical emergencies. However, thawed FFP may be re-labeled and stored as thawed plasma and refrigerated with a shelf life of up to 5 days. Plasma can also be processed and dehydrated to a stable powder of plasma proteins and rehydrated on demand (155). Lyophilized plasma may be stored for up to 2 years and can be safely deployed prehospital (156, 157). However, from our experience, it takes 10-15 minutes to rehydrate and reconstitute lyophilized plasma, and the procedure requires several steps. This is not optimal in time-critical emergencies. Finally, never frozen liquid plasma could be a viable alternative, allowing immediate availability and storage for up to 40 days. Liquid plasma contains lower levels of Factors V and VIII than FFP but is comparable to thawed plasma (158, 159, 160).

Platelets

Although neglected in resuscitation strategies for many years, platelets play a vital role in initiating hemostasis at the bleeding site. Once collected, platelets are usually stored under gentle agitation at room temperature. However, these storage conditions present a problem for prehospital providers. Further, platelets suffer even quicker from a «storage lesion» over time, especially at room temperature, impacting clinical outcomes (161, 162). Therefore, cold storage has been suggested to overcome the storage lesion and bacterial contamination. However, in the late 1960s, data demonstrated reduced *in vivo* viability of transfused cold-stored platelets (163). Today, it is appreciated that part of the explanation for the reduced circulating time of refrigerated platelets is that they are activated. As such, they migrate to the injury site and contribute to hemostasis. In addition, accelerated clearance of cold-stored platelets through the binding of Ashwell-Morrell receptors in the reticuloendothelial system has also been demonstrated. Still, this does not appear to affect hemostatic function in the acute setting (164). Indeed, in multiple clinical studies, cold-stored platelets have demonstrated hemostatic efficacy (165, 166). On the other hand, the hemostatic function of room-temperature stored platelets has been questioned (161). Hence, cold-stored platelets may be a viable option for prehospital resuscitation of hemorrhagic shock and have already been utilized in the U.S. and by overseas U.S. military units (167, 168).

Whole Blood

Whole blood can refer to two types of products. The first is warm fresh whole blood (WFWB), available as an option in austere environments for forward resuscitation (50, 169, 170). Over the last two decades, deployed military medical teams, especially special operations units, have implemented WFWB protocols (171, 172). The amount of equipment needed is limited to a collection bag, blood

administration set, blood typing cards, and point of care tests, making the protocol appealing for the special operations medic in the austere environment. However, WFWB is also utilized in civilian austere medical preparedness settings (173, 174). Typically, WFWB is drawn on an emergency basis from a selected and prescreened donor and transfused within a limited window (175). However, this procedure omits the standard pathogen screening usually performed on each blood unit before transfusion and blood group testing in the hospital. The risk of transfusion-transmitted disease and blood group mismatch can be mitigated by the utilization of a prescreened walking donor pool, preferably donors who are group O low anti-A and anti-B titer (LTOWB), in addition to robust protocols and point of care testing of TTD´s and blood groups (171, 176). Implementing WFWB protocols also requires extensive training and certification of the individual provider to ensure safety.

The second whole blood product refers to fully tested and standard refrigerated WB, usually termed cold WB (CWB). Depending on the anticoagulant used, it can be stored for 21 days (CPD) or 35 days (CPDA-1). This product may be maintained and monitored during prehospital storage with electronic temperature loggers and designated cooling boxes similar to what is used for PRBC. However, stored WB suffers from a «storage lesion» similar to PRBC. Platelets undergo shape change and lose function as they interact with fibrinogen and leukocytes, inducing the release of intracellular contents, leading to decreased function. The metabolic waste products accumulate, causing increased acidity. As such, the major concerns related to prehospital LTOWB are the potential reduced platelet function during storage and its consequences. In addition, the potential wastage due to relatively short storage times compared to erythrocyte concentrates is a potential concern. However, today, LTOWB is the only option that leaves the prehospital provider with a balanced transfusion option in one bag, ready for any patient at a moment's notice.

1.7. LTOWB as compared to BCT in RDCR, properties, and safety

When comparing BCT and LTOWB for hemostatic resuscitation, there are differences in hemostatic profile, logistical aspects, and safety issues that need to be considered.

In a reconstituted whole blood product made from 1:1:1 BCT, hemoglobin, hematocrit, and factor levels are lower than in the equivalent number of WB units. This is related to the amount of preservative solutions and anticoagulants in the individual bags of blood components compared to the single bags of WB. The differences may vary depending on the different protocols used internationally. Table 3. presents the properties of 1:1:1 BCT and WB, respectively, according to quality data from Haukeland University Hospital, Bergen.

	3 Units LTOWB	1:1:1 (3:3:1) Apheresis platelets	1:1:1 (3:3:1) Pooled platelets
Total volume	1362ml	1700ml	1783ml
Clear fluids content	177ml (13%)	452ml (27%)	496ml (28%)
Plasma volume	666ml (49%)	759 (45%)	798% (45%)
Erytrocytes	519ml (38%)	489ml (29%)	489 (27%)
Platelet concentration	165 x 10^9/L	167 x 10^9/L	174 x 10^9/L

Table 3. Overview of volume fractions in BCT and LTOWB

The table shows the total volume and volume fractions of the elements in LTOWB and 1:1:1 transfusions.

The ultimate differences in oxygen carrying capacity, factor content, platelet amount, and fibrinogen generate different *in vitro* physiological and hemostatic profiles. However, the clinical (*in-vivo*) relevance is still debated (177, 178). However, WB's superior oxygen-carrying capacity and hemostatic profile have appealed to prehospital services. Furthermore, during hemorrhagic shock, the

optimization of oxygen delivery and hemostatic potential underscores the argument that WB may be a more efficient and efficacious option (Fig.4).

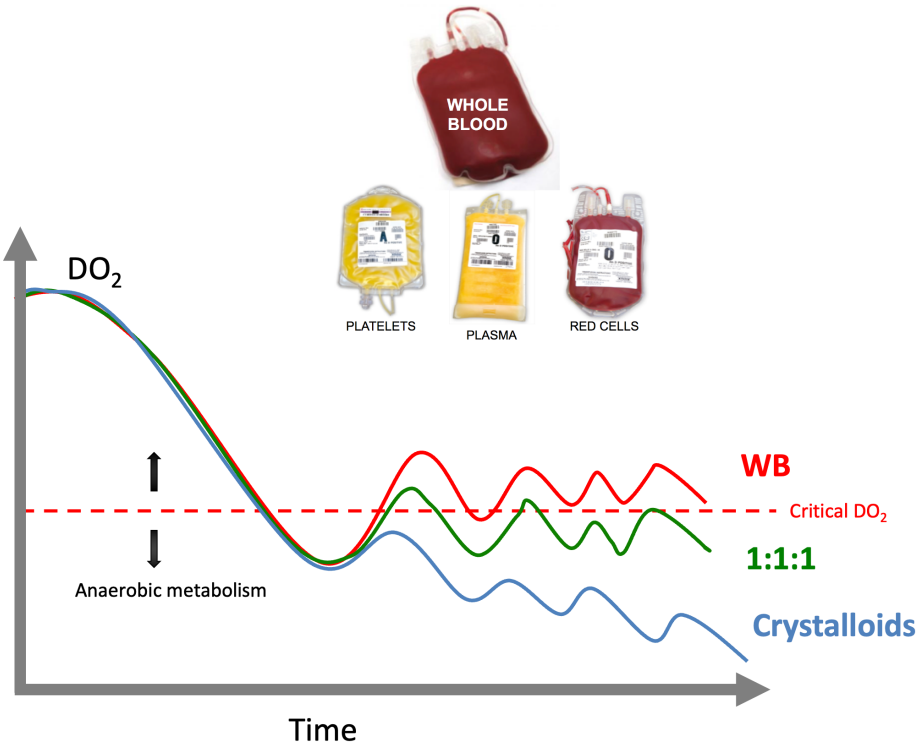

Fig. 4 The conceptual differences in oxygen-carrying potential during resuscitation of non-compressible hemorrhagic shock

The relative amount of additive solutions reduces the oxygen-carrying potential in 1:1:1 BCT compared to WB transfusion. As such, the hemoglobin concentration will ultimately stabilize at a lower level. Crystalloid therapy only contributes to increased DO_2 via a transient increase in cardiac output.

Laboratory studies have been performed to evaluate the coagulation potential of whole blood compared to 1:1:1 BCT. The results of these studies are in favor of whole blood (179, 180). However, it is difficult to compare the different products and strategies due to the impact of different storage durations of the individual

products. Further, *in vitro* coagulation assays and viscoelastic tests have limitations, and other factors than *in* vitro product quality influence the hemostatic potential of the products *in vivo* (181).

Concerning the logistics of resuscitation, it is much easier to collect, dispatch, transport, and transfuse single products rather than three different products with three different storage modalities. In prehospital resuscitation, other issues like limited resources and personnel, weight and storage constraints, and several competing time-critical tasks may limit the efficacy of BCT (182, 183). Further, providing the patient with a balanced transfusion in all phases of care with BCT might be challenging. This refers to the phenomenon mentioned above of «catching up,» The resulting consequence may be that resuscitation efforts are not balanced at all time phases.

1.8. Complications of transfusion

Although blood products and early hemostatic resuscitation may improve outcomes, they should be administered judiciously as several possible complications may occur. Whether relying on emergency release blood components or LTOWB, these complications may occur, with major hemolytic reactions following incompatible red cell transfusion and ABO mismatch being the most feared. The release of universal group O PRBC, group A or AB plasma, as well as LTOWB, may mitigate this risk. Other more common acute or delayed non-hemolytic transfusion reactions may occur but may be of minor importance in life-threatening hemorrhage.

For LTOWB, mitigation of possible hemolysis due to incompatible plasma when transfusing LTOWB to non-group O donors may be achieved by selecting donors with low anti-A and anti-B titers (184). However, there is still some debate on the

exact titer level that should be applied (e.g., <256 or <512) to ensure safety (185, 186). However, clinical experience and several trials have not been able to detect significant hemolysis. For example, one study found that at least four units of LTOWB with a titer <100 did not lead to hemolysis in trauma patients, and data from Haukeland University Hospital in Norway did not find evidence for hemolysis in patients receiving > 4 units (187, 188, 189, 190). A second issue is related to the amount of LTOWB provided that allows for a safe type-specific transfusion at a later stage. Again, further research is needed, but current protocols suggest continuing with type O PRBC or AB/A plasma after three to six units of LTOWB. Again, however, this is a subject for debate. Either way, this topic highlights the problem of obtaining the blood group of patients who have received massive transfusions pre-hospital and early in-hospital due to lack of pre-transfusion screening.

Transfusion-related acute lung injury (TRALI) is a rare but serious complication following transfusion that is characterized by sudden onset of respiratory distress not attributable to another cause (191). All plasma-containing blood products have been implicated in TRALI. It is thought to be caused by the activation of the recipient's neutrophils via human leukocyte antigens (HLA) or human neutrophil antigens (HNA) by donor-derived antibodies. Females with a history of pregnancy have a higher risk of anti-HLA/HNA antibodies. Some jurisdictions have adopted mitigation strategies to prevent TRALI. These include the utilization of male donors for universal blood components or LTOWB or anti-HLA and HNA testing. Theoretically, LTOWB transfusion would decrease the risk of TRALI due to the relative exposure to fewer donors during the course of resuscitation.

A second common complication of blood transfusion is transfusion-associated circulatory overload (TACO). Typically, the patient presents with respiratory distress due to developing pulmonary edema due to volume excess or circulatory overload following transfusion. Aggressive over-resuscitation with BCT or WB in

patients suffering from hemorrhagic shock may contribute to the development of TACO, underscoring the need for monitoring and constant reevaluation of the clinical condition.

Efforts should be made to transfuse Rh-negative LTOWB or PRBC to female recipients of unknown blood type in the fertile age groups to avoid alloimmunization to the D antigen in Rh-negative individuals. However, the risk of alloimmunization in patients suffering from hemorrhagic shock is low. As such, some situations may warrant Rh-positive blood transfusion to recipients of unknown blood type and even, in some circumstances, to patients who are known Rh-negative (192). In Norway, blood transfusion policies seek to reduce the risk of hemolytic disease of the fetus/newborn in future pregnancies by administering Rh-negative blood to this population. However, some institutions ignore this for patients in hemorrhagic shock due to the limited availability of Rh-negative donors and the overall cost-benefit analysis in this population (193, 194).

When transfusing universal group O red cells, there is a risk of clinically significant alloantibodies outside the ABO blood group system. Sensitization to these erythrocyte antigens is influenced by the number and frequency of prior transfusions, earlier pregnancies, the recipient's age, sex, and potential comorbidities. However, the risk of clinically significant immediate or delayed transfusion reactions seems to be low in most patients presenting to the ED (195).

1.9. Why is this thesis needed?

To salvage a patient that presents with severe non-compressible hemorrhage is dependent on a multitude of factors ranging from the urgent response and timely critical interventions by capable pre-hospital care providers, swift evacuation, timely assessment and stabilization in the hospital, emergency surgery or other

hemostatic interventions to achieve hemorrhage control, complicated ICU care and ultimately rehabilitation. The initial workload in these «damage control» - pathways may be challenging. As such, the resuscitation strategy should be simple and effective. In this context, several civilian and military EMS are now investigating opportunities to implement WB, yet its use is still controversial and debated. Establishing a robust system for forward resuscitation with WB is challenging. There is limited data available on the implementation of WB programs in Europe. The renewed interest in WB in this context warrants a description of the implementation process and an evaluation of the safety, feasibility, and logistics of using WB in RDCR. Further, it is especially important to assess the properties of WB, evaluate its clinical use, and identify and address potential barriers to facilitate early resuscitation.

This thesis addresses the barriers that may obstruct early prehospital resuscitation with whole blood, such as immediate access to the vascular system during hemorrhagic shock. Further, there is limited data on the product quality, efficacy, and safety of forward-stored LTOWB. Lastly, the thesis will describe and evaluate the safety of forward resuscitation of hemorrhagic shock with WB in a Scandinavian HEMS system and identify obstacles in implementing WB in other EMS systems in Norway.

2. Aims of thesis

2.1. General aim

The overall primary aim of this thesis was to identify challenges in the forward resuscitation of hemorrhagic shock and explore and evaluate potential solutions. In addition, the thesis aimed to identify potential barriers to implementing a prehospital LTOWB program and to describe and review the implementation in a Norwegian HEMS (Fig.5). This was achieved by using different methodological approaches as outlined in the specific aims.

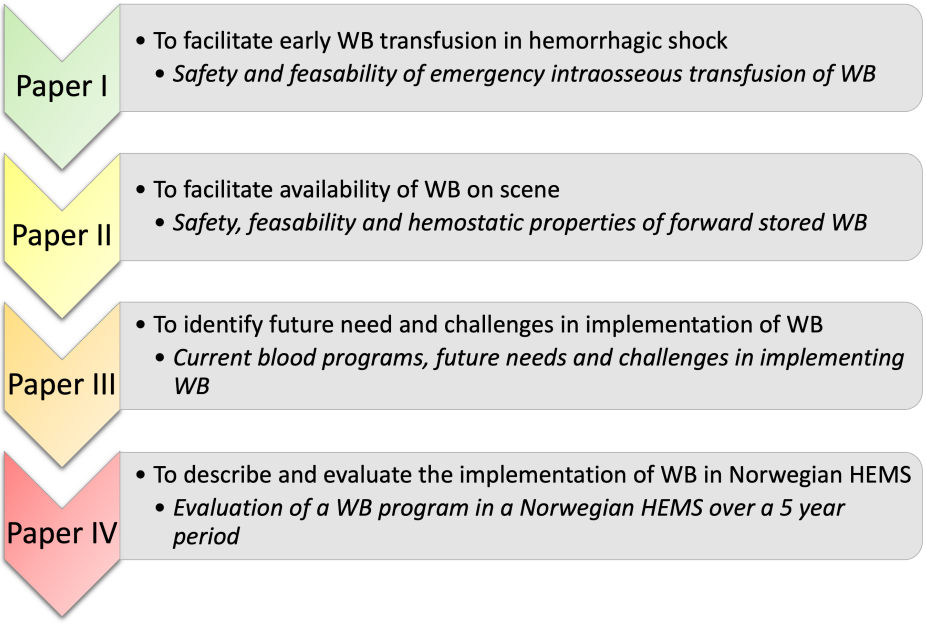

Fig. 5 Aims of thesis

Figure 5, an overview of the aims of the thesis

2.2.Specific aims

Paper I

The primary objective was to compare flow-rate of re-infusion of WB using the sternal intraosseous route compared to the intravenous route using two different CE-marked and FDA-approved emergency sternal intraosseous devices and to measure post re-infusion hemolysis using haptoglobin and lactate dehydrogenase (LDH) as the primary marker for hemolysis.

A secondary objective was to compare the technical success rate of sternal access between the two devices and to evaluate the feasibility of using the sternal intraosseous route for emergency WB transfusions.

Paper II

The primary objective was to assess *in vitro* quality of WB during storage for up to 21 days when stored in an airtight storage container forward at the operating base as compared to WB stored in the blood bank.

A secondary objective was to establish a storage protocol for the forward handling of CWB and to evaluate if storage conditions met EU standards.

Paper III

The primary objective was to describe Norwegian prehospital air ambulance blood transfusion programs.

A secondary objective was to identify future needs for the implementation of LTOWB, describe the rationale for LTOWB in Norway, and identify potential implementation obstacles.

Paper IV

The objective was to describe and evaluate the implementation of LTOWB in a Norwegian HEMS system, with primary endpoints being the number of transfused patients, transfusion-related adverse events, and survival rates.

3. Materials and methods

In this section, I will present an overview of the selected methods. For comprehensive details regarding study design, study population, and the technical aspects of the chosen methods, I refer to the respective papers.

3.1. Paper I

Design

This was a prospective non-randomized three-armed comparative study.

Subjects and sample size

Volunteer military personnel who attended the Norwegian Naval Special Operation Commando training in RDCR were enrolled after written informed consent. Warm fresh whole blood was collected and re-infused using two different sternal intraosseous devices (EZ-IO T.A.L.O.N and FAST-1) and a standard 18G intravenous line. A total of 30 participants were enrolled, 10 in each group.

Intervention and procedures

Baseline blood sampling was performed before blood donation. Blood was collected in standard CPDA-1 bags and placed on a blood collection mixer. The bags were stored for up to 20 minutes awaiting re-infusion.

The participants performed the IO procedure under supervision. The IO needles were placed in the manubrium of the sternum according to the manufacturer's instructions. Correct placement was confirmed with aspiration of

bone marrow, followed by rapid flushing of 0.9% sodium chloride. The IV cannulas were placed in the left or right antecubital vein.

Re-infusion was performed through a standard blood administration set with 180cm of tubing connected to a three-way connection tube. Re-infusion was performed with gravity only, without additional pressure on the collection bags with subjects supine. In the IO groups, rapid flushing with 2mL of 0.9% sodium chloride was repeated if the provider considered flow to be inadequate. Thirty minutes after completion, post re-infusion blood samples were collected. Investigation of hemolysis was performed by measurement of haptoglobin and lactate dehydrogenase. The number of failed IO insertions, total re-infusion time, number of flushing procedures, and pain associated with the procedure were noted.

Statistical analysis

Test of the distribution of variables was performed using the Shapiro-Wilk test. Due to the overall non-normal distribution of variables, comparisons were performed using Kruskal-Wallis nonparametric tests (for three group comparisons), Wilcoxon signed rank test for related samples, and Mann-Whitney U test for two independent samples.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK 2014/691) and registered in the ClinicalTrials.gov registry (NCT02924792).

3.2. Paper II

Design

This was a prospective two-armed observational study.

Subjects and sample size

Twenty WB units (test) were stored in an airtight thermal container and deployed on missions at Bergen HEMS for seven days. After seven days, units were rotated back to the blood bank for additional storage of 14 days (total storage time 21 days) in the container. Twenty WB units (control) were stored in a conventional, approved, and monitored refrigerator at the blood bank for 21 days. There were no previous studies that could be used for power calculation. Based on a general assumption of normality for outcome measures, enabling the use of a two-sided t-test, setting the mean to 1 and standard deviation to 0.5, with a significance level of 0.05 and a power of 0.8, we found that we needed a minimum of 17 units in each group. Hence, we choose to have 20 units in each group to ensure the completion of the study with adequate power.

Collection and preparation of WB units

WB was collected from regular healthy volunteer low titer group O blood donors using a 450ml CPD collection set. The units were filtered through an inline PLT-sparing leukocyte-reducing filter allowing for a PLT content of more than 90% of the unit before filtration and a white blood cell (WBC) concentration of 1 x 10^6/ unit.

Cold chain maintenance and forward monitoring

The test group WB units were transferred to an approved, primed, and conditioned portable thermal container (Crédo Duracube HD, with a Golden Hour inner container, Pelican Biothermal) together with a data logger that recorded ambient temperature, humidity, light, and three-axis acceleration. The thermal container was conditioned at -18°C followed by a staging at 22ºC before adding the WB units. The thermal container was stored in a regular refrigerator at the HEMS base

and carried on missions for seven days before returning to the blood bank, followed by an additional 14 days of storage in the container at the blood bank.

Laboratory investigations

Samples were collected on days 1,8,14 and 21. Laboratory investigations included hematology parameters, blood gas variables, and coagulation parameters. The hemostatic function was evaluated with kaolin-initiated thromboelastography, multiple impedance aggregometry, and light transmission aggregometry for platelet function. In a subset of test and control units, platelet activation and adhesion were investigated by flow cytometry.

Statistical analysis

The effect of forward storage of LTOWB in an airtight container on each of the outcome variables was investigated using a linear mixed effects model. Storage time, study group, and their interaction were used as predictors. Simple contrasts were used to investigate whether the variables changed from days 1-8, 1-14, and 1-21. The interaction between storage time and study group was used to describe whether the change was different between blood stored at the HEMS or blood stored in the blood bank.

Ethics

There were no patient interventions in the study. However, WB units were enrolled after written informed consent from all donors. The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK 2017/157)

3.3. Paper III

Design

This was a national survey of prehospital blood transfusion programs in HEMS.

Subjects

All medical directors for the HEMS and Search and Rescue (SAR) helicopter bases in Norway were invited to participate in the survey. In addition, all blood banks that support HEMS with LTOWB were invited to participate.

Data collection

The medical directors from the 13 HEMS and 7 SAR bases were contacted by telephone, and the survey aims were outlined. An electronic questionnaire was sent by email following the telephone call. A similar approach was applied to the blood banks.

Three different questionnaires were used in the survey. One questionnaire for the HEMS who had implemented LTOWB, a separate questionnaire for those who had not, and a third questionnaire for blood banks that supported LTOWB to the HEMS in their region. Different questionnaires were used to gather specific data on the experience of the use and the supply of LTOWB.

Ethics

No patient information was collected. The local data protection officer at Haukeland University Hospital reviewed the study.

3.4. Paper IV

Design

This was a prospective observational study.

Population

Over a five-year period, patients who suffered from hemorrhagic shock and received prehospital transfusion with LTOWB, FDP, or PRBC from Bergen HEMS were included.

Endpoints

Primary endpoints were the category and number of patients transfused, transfusion-related adverse events, and 24h/30-day survival. Secondary endpoints were HEMS response times, key vital signs, and emergency interventions.

Data collection

Prehospital data was collected by the attending HEMS physician. In-hospital data were obtained from patient records and the blood bank management system.

Injury/illness severity

The severity of the condition was classified using the National Advisory Committee on Aeronautics (NACA) severity score since both non-trauma and trauma patients were included.

Blood products and logistics

Two LTOWB units were collected weekly at the Department of Immunology and Transfusion Medicine (Haukeland University Hospital, Bergen). The units were stored in primed thermal containers and carried on HEMS missions. Between missions, the containers were stored inside a standard refrigerator. If unused, the units were rotated back and stored for up to 21 days awaiting in-hospital utilization in massive transfusion packages. If the units were used at the HEMS, immediate replacement of LTOWB or PRBC units was facilitated. The HEMS service also carried an additional unit of FDP.

Statistics and data presentation

Data were presented as medians with interquartile ranges or means and standard deviations. Categorical variables were presented as numbers with percentages of the total. The Wilcoxon signed-rank test was used when comparing prehospital and in-hospital vital signs.

Ethics

Written informed consent was obtained from surviving subjects. The consent covered patient data acquisition and handling from the time of emergency intervention to the last endpoint and subsequent data handling and storage. Informed consent was waived for deceased subjects. The Regional Committee for Medical and Health Research Ethics in Norway approved the study (REK 2016/304), and the study was registered in the ClinicalTrials.gov registry (NCT02784951)

4. Summary of main results

The summary of results in this thesis is abridged with full reference to the appended papers I-IV.

4.1. Results paper I

In the intraosseous reinfusion study, a total of 36 participants were enrolled. Six participants were excluded; two due to failure in the blood collection procedure and four due to failure of the IO procedure. In the T.A.L.O.N. IO group, 4 (29%) of the 14 procedures failed. In the Fast-1 IO group, 1 (9%) of the 11 procedures failed. One of the participants in the failed T.A.L.O.N group was moved to the IV group.

The participants were all male, with a median age of 25, 27, and 34 years in the Fast-1, T.A.L.O.N., and IV group, respectively. Baseline hemoglobin, haptoglobin, platelet count, and lactate dehydrogenase (LD) levels were within normal ranges in all subjects.

The median reinfusion rate was 46.2 (39.3-51.2) mL/min in the Fast-1 IO group, 32.4 (26.3-39.3) mL/min in the T.A.L.O.N. IO group, and 74.1 (72.0-84.8) mL/min in the IV group. There were statistically significant differences between all groups ($p<0.05$).

Between-group analysis of the median change in hemolysis parameters showed no statistically significant differences.

Within-group analysis of the change in hemolysis parameters and hemoglobin before and after reinfusion showed a significant elevation of LD in the Fast-1 group 174 (155-216) to 176 (156-242) U/L ($p<0.05$). No decrease in haptoglobin or significant changes in Hb was observed in this group. In the T.A.L.O.N group,

there was a significant change in Hb from 15.8 (15.1-16.3) g/dL to 15.45 (14.9-16.2) g/dL. In the IV group, haptoglobin decreased from 0.88 (0.70-1.34) g/L to 0.86 (0.68-1,31) g/L.

As such, we found an infusion rate of 46.2 mL/min (Fast-1) and 32.4 (T.A.L.O.N.) and no evidence of clinically relevant hemolysis.

4.2. Results paper II

A total of 40 CWB units were monitored and tested. Twenty units were dispatched, stored at the HEMS base, and brought on missions, and twenty served as control. During forward storage, there were no recorded breaches in temperature limits (1-10ºC). The CWB units were carried on a mean 4.1 (2.86-5.34) number of missions, and the mean time outside the refrigerator in the thermal box was 339 (209-469) minutes. Figure 6. shows the hematology, clinical chemistry, and hemostatic capacity of CWB during storage at the HEMS and blood bank.

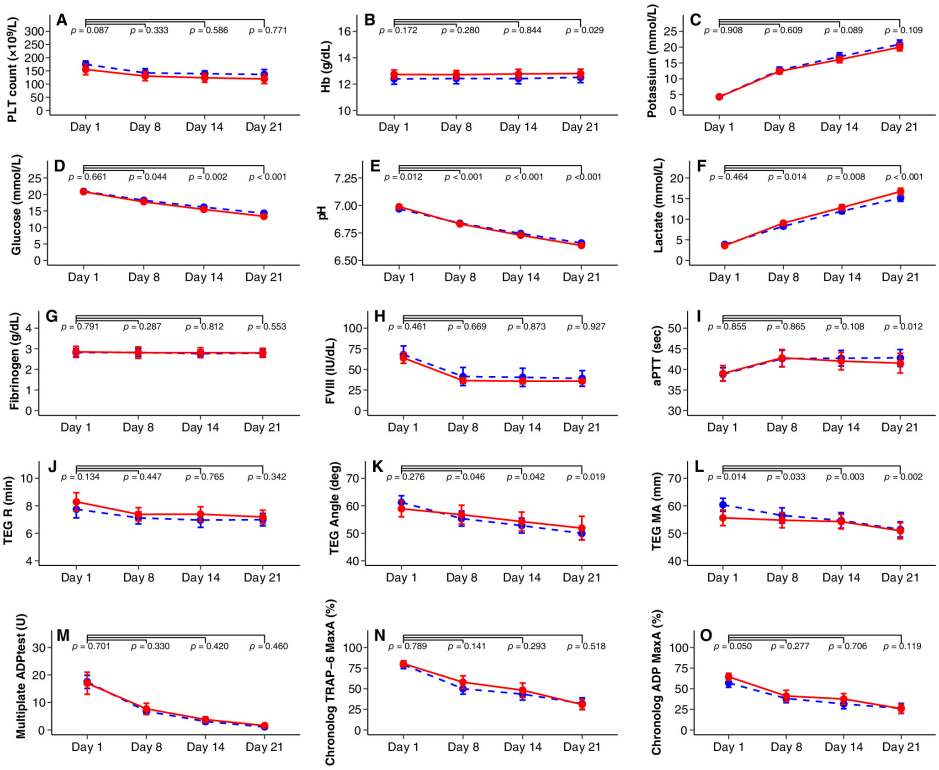

Figure 6. Hematology, clinical chemistry, metabolism, and hemostatic properties of cold-stored LTOWB as compared to LTOWB stored in the blood bank.

Mean and 95% CIs of the variables during 21 days of storage. (- - - -) Control group; (——) HEMS group. A linear mixed-effects model was fitted with storage time, study group, and their interaction as predictors. The p-value shown represents the interaction between storage time and study group and signifies whether there was a significant difference between the two groups in how the variable changed from Day 1 to 8, Day 1 to 14, and Day 1 to 21. Reprinted with permission from John Wiley and Sons, License Number: 5460970292046

There was a significant difference in the change of Hb levels in the two groups from day 1 to day 21. Regarding metabolism parameters, the glucose concentration declined more in the CWB units stored at the HEMS base on days 8,14, and 21 compared to the control group. The same was evident with regard to base excess (BE) and pH. Conversely, lactate increased more in the HEMS group within the same timeframe.

When assessing the hemostatic properties, the TEG angle and maximal amplitude (MA) declined less in the HEMS units on days 8,14, and 21. There were no differences in platelet aggregation capacity between the two groups as measured by multiple impedance and light transmission aggregometry. Lastly, flow cytometry measured no difference in platelet function as measured by investigating ADP and TRAP-stimulated expression of CD62P and CD42b.

We conclude that all CWB units complied with EU standards throughout storage in both groups. There were no significant differences in PLT aggregation, viscoelastic properties, and hematology variables between the two groups. However, minor yet significantly lower pH, glucose, base excess, and higher lactate were observed after storage in the airtight containers.

4.3. Results paper III

All medical directors from the 13 HEMS, seven SAR bases, and the four blood banks providing LTOWB responded to the survey. The inventory of the services is outlined in figure 7.

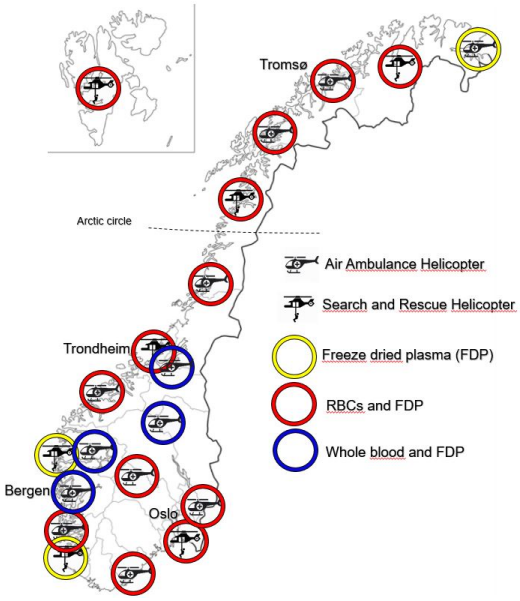

Fig. 7 The location and blood inventory of HEMS and SAR helicopter bases in Norway.

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All services reported that they carried various hemostatic adjuncts. Tranexamic acid (100%), fibrinogen concentrate (30%), prothrombin complex concentrate (10%), and calcium chloride/gluconate (80%). All but one base stored blood at the base.

In 2020, there were 216 prehospital transfusion episodes in the SAR and HEMS services, as outlined in figure x.

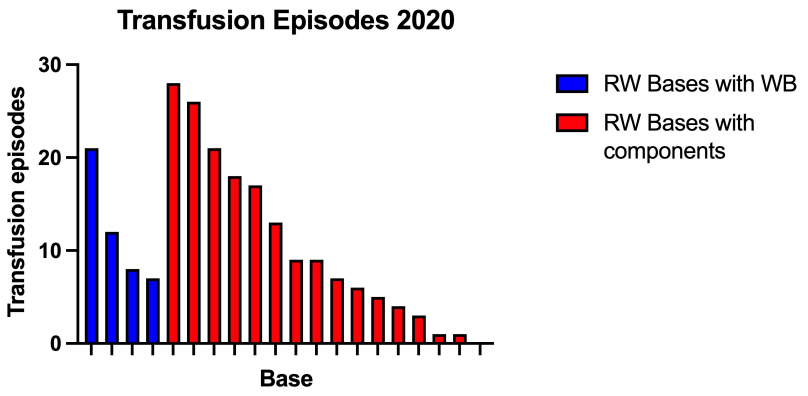

Fig. 8 Transfusion episodes in HEMS and SAR - 2020

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Most services (14/16 - 88%) stated that they wished to explore and implement a WB program in the future. The medical directors that had requested LTOWB from their local blood bank reported several obstacles, including:

- LTOWB not currently available at the local blood bank
- The need for further evidence on the efficacy and safety of prehospital LTOWB transfusions programs
- Negative cost/benefit analysis due to few potential transfusions, including the potential for waste
- The lack of potential LTOWB donors

Conversely, the medical directors from the HEMS bases that deploy LTOWB reported that the appealing factors of LTOWB were that each bag carries a greater volume than BCT, that the product is less hemodiluted and can provide a balanced transfusion strategy early and thus ease the logistics of resuscitation. In addition, the logistical burdens of the LTOWB programs were reported as low.

The blood banks that supported LTOWB all provided Rhesus-D negative LTOWB. The definition of «low titer» varied between the blood banks. Three blood banks defined low titer as follows; IgM anti-A and anti-B <256 and IgG anti-A and anti-B < 500. The last blood bank defined low titer for IgM and IgG <256. Two of the blood banks included both male and female donors, and the others male only. Three of the blood banks stated that they had sufficient LTOWB donors for the transfusion program, but the last reported difficulties in recruiting donors from time to time. The storage time on the HEMS was reported to be seven days at two bases and 14 days at two. Unused blood was utilized for in-hospital patients in two centers; for the others, the units were discarded. Wastage rates were reported to be 79.6%, 73.2%, 77%, and 26.4%, respectively. The lowest rate was reported at the hospital that utilizes LTOWB in the massive transfusion package in-hospital.

In summary, we found that all SAR and HEMS services in Norway have hemostatic resuscitation capabilities. As of July 2021, four services have implemented LTOWB. Most services prefer LTOWB, mainly due to the logistical benefits. Blood banks that provide LTOWB report favorable experiences with LTOWB.

4.4.Results paper IV

HEMS responded to 5124 patients in the five-year period, as presented in figure 9.

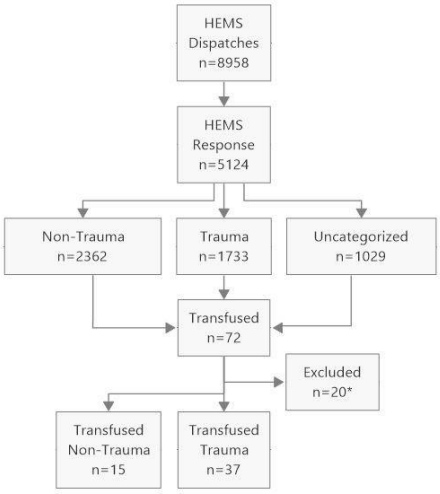

Fig. 9 Total number of HEMS dispatches and the number of responses by category.

Seventy-two patients were transfused in this period. Twenty patients were excluded, 16 due to lack of informed consent, and four were excluded since they did not meet inclusion criteria. Reprinted with permission according to Creative Commons license 4.0.

Data were analyzed from 52 patients with a mean NACA score of 5.63 (SD 0.864). The dataset included 41 (79%) males and 11 female (21%) patients with a median age of 49 (IQR 27-70). The most prominent mechanisms of injury and illness were motor vehicle accidents (26.9%), falls from heights (15.4%), gastrointestinal bleeding (15.4%), ruptured aorta (9.6%), and penetrating injuries/stab wounds (7.7%).

There were no reported adverse events related to the transfusion procedure or suspected clinical transfusion reactions. In 90% of the cases, there were no reported problems related to the transfusion procedure; however, in two cases (4%), there were problems with the IO procedure delaying transfusion. In three other cases, the teams experienced difficulties achieving intravenous access, missing transfusion sets, and overt pain during the transfusion of cold WB, respectively.

Of the 52 patients, 48 (92%) received LTOWB, 9 (17%) received PRBC and 9 (17%) FDP.

Twenty-eight patients survived beyond 30 days. Thirty-six (69%) survived 24 hours. Of the 24 deaths (46%), six (12%) died within one hour, seven (13%) died within 6 hours, and three (6%) died within 24 hours. The remaining eight patients died within 30 days. Ten (19%) patients presented with cardiac arrest on scene; four of these were admitted to the ED with signs of life. No patient who presented with cardiac arrest on scene survived beyond 24 hours.

Thirty-five of the 46 patients who were admitted to the hospital alive received additional transfusions of blood components or whole blood in the first 24 hours.

Of the 42 patients who did not present with cardiac arrest on scene, 24 (57%) had a documented blood pressure before transfusion. The others were assessed with peripheral or central pulses. In five patients, there were no documented assessments of blood pressure or pulses. Median Glasgow Coma Scale (GCS), systolic blood pressure, and heart rate were 9.5, 80, and 80, respectively.

All cardiac arrest patients received advanced airway management. Nine (21%) of the non-cardiac arrest patients received rapid sequence induction and endotracheal intubation on scene. Three (7%) received bag-mask ventilation, and 17 (40%) were provided with supplemental oxygen on a nonrebreather mask. Thirteen patients (31%) received no airway management or supplemental oxygen.

The median response time was 20 minutes (IQR 12-35) on primary missions and 37 (IQR 20-43) on inter-hospital transfer missions. The median on-scene time for primary and secondary missions was 7.5 minutes (IQR 4-19) and 15 (IQR 9-24), respectively. Transport times were 19 minutes (IQR 12-26) for primary missions and 35 minutes (IQR 20-41) for secondary missions.

Of the 46 admitted patients, 41 received emergency interventions at the hospital within the first 24 hours. In-hospital interventions included thoracotomy, laparotomy, craniotomy, skin sutures of major soft tissue lacerations, radiological hemostatic interventions, bone fracture repairs, or hemostatic gastroscopies.

In summary, 1,4% of patients were transfused during the five-year period. Most patients presented with blunt trauma mechanisms and hemorrhage unrelated to trauma. No transfusion reactions, complications, or logistical issues were reported. Overall 69% of the patients survived 24 hours, and 54% survived 30 days.

5. General Discussion

This dissertation identifies challenges in forward resuscitation of hemorrhagic shock, including timely access to the vasculature with intraosseous devices for WB transfusion, as well as the potential challenges in making LTOWB available on scene. We present data on the feasibility, efficacy, and safety of WB transfusion via the sternal intraosseous route, as well as the implementation and product quality of forward-stored LTOWB. The dissertation presents data on potential obstacles in implementing LTOWB in Norwegian HEMS and SAR helicopter services and presents data on a LTOWB program in a HEMS system in the western part of Norway.

5.1. Methodological considerations

In this section, I will discuss the rationale for the study design and describe the selected methods and their limitations.

The aim of paper I was to explore the safety and feasibility of emergency intraosseous transfusion of WB. The available evidence on intraosseous blood transfusions was based on animal studies, theoretical modeling, and individual case reports with conflicting results (196, 197, 198, 199, 200). In addition, live training with autologous re-infusion of WFWB is performed regularly, especially in military special operations medical training. Although some case reports and animal studies were available, we decided that a prospective comparative human study would be needed to explore the safety and efficacy of the procedure. Due to the lack of available data, we could not perform precise power calculations. Because the literature describes potential harm caused by additional pressure during infusion, we decided to evaluate re-infusion using gravity alone. Our data

support that adequate flow rates may be achieved without additional pressure. Hence, with this study design, we could not rule out hemolysis during high-pressure re-infusions, often performed in clinical practice. It is also important to realize that the study investigates the reinfusion of WFWB, which has a lower hematocrit than PRBC. The elevated hematocrit and lower temperature may cause flow-related problems in PRBC transfusions.

In paper II, we compared forward-stored WB and WB stored in the blood bank. In addition to regular hematologic, biochemical, and metabolic parameters, we sought to investigate hemostatic function in depth. There are a lot of quality assurance data on the in-house storage and transfer of blood and blood components (201, 202, 203). In addition, European directives and guidelines define how to store and handle the products safely, as well as regulations on product quality (204). However, to our knowledge, there was no published data on the logistics and safety of forward storage of LTOWB in a HEMS environment. We decided that a prospective two-armed comparative study was suitable to compare storage conditions and product quality during storage. One of the primary considerations was to investigate the storage conditions in clinical practice rather than in a simulated environment. A linear mixed effects statistical model with storage time and storage conditions and their interaction as predictors was chosen due to the longitudinal design and repeated measurements. As such, we were able to use simple contrasts to investigate whether the outcome variables had changed at the different time points and to describe whether the level of change was different between the groups. Viscoelastic testing was chosen due to the ability to measure whole blood's capacity to form a clot quantitatively. Viscoelastic point-of-care coagulation testing has been used in trauma and surgical settings to manage goal-directed therapy of blood component transfusions and assessment of coagulopathy. It provides a holistic view of *ex vivo* clotting, examining red cells, platelets, fibrin(ogen), coagulation factors, and medication contribution to clotting. The assay used in paper II (TEG 5000) measures the physical clot formation during the

transition of blood from a liquid to a gel state by assessing the clot shear modulus using physical force transduction by a pin suspended in a cup of whole blood. A clotting activator is added (kaolin), and as the clot forms around the pin and the cup walls, the opposing forces in the rotation of the cup are measured and displayed continuously in the thromboelastogram providing information on the kinetics of clot formation, clot strength, and potential fibrinolysis. The clot initiation time (R-time) is dependent on the concentration and function of coagulation factors. The kinetics of clot formation (α -angle, K-value) is dependent on fibrinogen levels and platelets. The clot strength (Maximal Amplitude, MA) depends on the platelet abundance, fibrin cross-linking, and clot retraction. At last, the lysis (LY 30) describes the fibrinolysis stage, dependent on the level of plasmin and plasminogen (111, 205). We choose to utilize rotational thromboelastography (TEG 5000) in our study. The alternative option was rotational thromboelastometry (ROTEM). Although similar, they report metrics with different nomenclature. Unlike TEG, ROTEM has four separate channels with different reagents that can detect abnormalities in different compounds involved in coagulation (Intem -contact activation pathway, Extem - tissue factor pathway, Heptem - neutralization of heparin, and Fibtem - fibrinogen contribution) (206). It is important to note that the clinical relevance of the thromboelastography and platelet function findings is disputed as it measures blood coagulation *ex vivo*. *In vivo* coagulation is much more complex as the tissue factor, size of the injured vessel, blood flow characteristics, and local vessel wall biology will affect the *in vivo* formation of a clot.

Due to the ongoing debate on the platelet function in CWB, several modes for investigating platelet function were chosen (multiple impedance aggregometry, optical aggregometry, and flow cytometry) (207). Optical aggregometry is considered the «gold standard» of platelet function testing. It is based on detecting the difference in light transmission after adding a platelet agonist to platelet-rich plasma. Different platelet agonists may be used. We chose the thrombin receptor

activating peptide (TRAP) and ADP to assess the potential acquired platelet function dysfunction during storage. In addition, we performed impedance aggregometry testing of platelet function using the same agonists as stimulants. This method measures the change in electrical impedance between two electrodes during platelet aggregation; an increase in electrical impedance corresponds to platelet aggregation. This method assesses platelet function more physiologically as it measures aggregation in whole blood, enabling other elements to influence the aggregation response. At last, flow cytometry was used to assess the expression of surface CD62p quantitatively as a measure of the unstimulated platelet activation in the two groups to evaluate how storage conditions influenced platelet activation (208). In addition, platelet activation potential was assessed with the expression of CD62p with ADP and TRAP as stimulants.

Over the last decade, there have been several changes in prehospital hemostatic resuscitation strategies in Norway. In paper III, we used a simple survey amongst the end-users and supporting blood banks to gather data on the utilization, rationale, logistics, and future perspectives of pre-hospital blood and blood products in Norway. The medical leadership and administration of the individual HEMS and SAR helicopter services differ in their opinions on transfusion strategies. As such, we concluded that a survey amongst the medical directors at the individual base would give further insight into the regulatory obstacles in the different transfusion programs. Further, a survey among the medical directors would provide a higher response rate and more detailed information. A more comprehensive survey amongst all medical doctors in the SAR and HEMS services would probably give more information on the different attitudes and rationale of RDCR, but the response rates would likely be poor and biased. In Norway, the Blood Transfusion Service is organized as individual government-funded blood banks located at the different hospitals. The inventory of blood differs between the blood banks based on local policies. To give further insight, we also decided to include the blood banking perspective.

Paper IV aimed to describe and evaluate the implementation of LTOWB in a Norwegian HEMS service. As mentioned earlier, patients in extremis suffering from hemorrhagic shock are quite rare in Norway, but prospective observational data may contribute to the overall evidence in this field. In 2015, the intention was to collect data on all prehospital transfusions in Norway. The prospective design allowed for more detailed and defined information on the endpoints in these patients. In addition, the prospective design was chosen to generate new hypotheses and provide data for future randomized controlled trials. We decided to evaluate current clinical practice in a physician-staffed HEMS in Norway. Hence transfusions were administered in compliance with the local HEMS standard operating procedures. Further, due to the suspected small number of patients during the five-year period, we decided to include both non-trauma and trauma victims to highlight the overall appearance of a LTOWB transfusion program in a Norwegian HEMS.

5.2. Discussion

The Norwegian prehospital medical services cover a population of 5,5 million living in a country with challenging topography, including mountain areas and fjords. In addition, the approximate distance of 600km between the level-one trauma hospitals illustrates the need for air transportation systems and remote damage control resuscitation protocols. In the last decade, there has been a paradigm shift to include hemostatic considerations in prehospital resuscitation strategies. Today, all Norwegian HEMS and SAR services provide WB or BCT to patients (paper III). Although to a lesser degree, this shift is also evident in EU prehospital services (147). In this thesis, we have found that early intraosseous hemostatic resuscitation with WB may be initiated efficiently and safely. LTOWB may be stored forward and brought on missions for up to 21 days. Forward-stored blood complies with EU regulations, and the hemostatic potential is present during

storage. The thesis has found favorable experiences with the utilization of LTOWB both from the blood bank and end-user perspectives. The logistics of LTOWB transfusions are manageable and safe.

Intravenous administration of medication, fluids, and potentially blood for hemostatic resuscitation is one of the key concepts of emergency care. Further, the optimal time for achieving vascular access has been disputed. Studies address delays of up to 5 minutes owing to the cannulation procedure (118, 209). In patients suffering from hemorrhagic shock, cannulation may be even more complex. Several EMS systems support the «load-and-go» doctrine in severe trauma, favoring only critical interventions on scene and cannulation in the emergency department (210, 211). This approach might be reasonable for services that do not carry blood, but EMS systems deploying blood to the scene should achieve vascular access early to initiate hemostatic resuscitation.

Intraosseous vascular access is an alternative technique for achieving vascular access through the non-collapsible venous plexuses in the bone marrow (212). However, the evidence for utility in blood transfusion has been questioned. Concerns about the flow of viscous blood through the porous bone marrow causing hemolysis and the claimed inadequate flow rates for hemostatic resuscitation are leading some to conclude that the IO route is contraindicated for blood transfusions (197). The potential limited flow is hypothesized to be caused by the need to overcome the intraosseous pressure (1/4 of arterial pressure) and by the physiological principles of Darcy's law, which describe the inverse relationship between blood viscosity, bone density, and rate of flow (197, 213, 214). The subsequent need for increasing IO infusion pressures to achieve adequate flow could potentially cause shear forces that cause hemolysis, especially in patients between 20-40 years, the age group that presents with the highest bone densities (197). This is contrasted to the clinical use of IO access for resuscitation of trauma

victims both in the civilian and military populations (215, 216, 217). However, only a small number of animal studies address this matter. These studies have presented conflicting results regarding the flow rate and have not found clinically relevant hemolysis unless pull-push infusion techniques with a syringe were applied, reaching infusion pressures >3000-4000mmHg (196, 198, 200, 218).

Although our data show lower flow rates compared to a standard peripheral IV line, IO transfusion rates are sufficient to maintain the flow needed to fulfill the criteria for massive transfusion (219). Hence, the data show that it should be possible to administer one unit of WB within 11 minutes with no other pressure than gravity. Most prehospital services carry only two units of blood, and the evacuation time seldom exceeds 20 minutes (papers III/IV). As such, the IO transfusion rates achieved are sufficient and suitable for the immediate prehospital resuscitation of hemorrhagic shock. There was no evidence of hemolysis in study I, which is consistent with earlier animal studies. The observed change in Hb and LD was of no clinical significance. There were differences in the success rate of the different IO devices, and it is worthwhile mentioning that most providers did not have experience with the procedure. Nevertheless, only one out of eleven procedures failed with the FAST-1 device. These data correspond with earlier reports' high success rates (220). Due to the superior flow rates, the sternal access may be an attractive access site for resuscitation of hemorrhagic shock. In addition, the marrow cavities of the manubrium and sternal body seldom communicate, allowing for patent use even in the case of sternum fracture (38). This is not the case for distal fractures and IO access sites in the humerus or tibia. On the other hand, sternal IO devices may be cumbersome to handle in cardiopulmonary resuscitation settings. In time-critical hemorrhagic shock, sternal IO access may be achieved in 30-60 seconds and is an alternative to the problematic prehospital IV cannulations. This ultimately may facilitate early resuscitation with WB or BCT and short on-scene times.

In the case of non-compressible hemorrhage, RDCR principles dictate early resuscitation and moving as fast as possible to definitive hemorrhage control in the hospital. Over the last decade, as outlined in paper III, most HEMS services have shifted policy to carry LTOWB or BCT to respond quickly. It would represent a significant time delay for the HEMS to pick up blood at the blood bank when needed. However, the forward storage of LTOWB differs from the blood storage in the blood bank. Maintenance of the temperature conditions at the base, in-flight, and on-scene requires a robust «cold chain» and may be achieved using portable thermal boxes (221). We found that the storage protocol facilitated storage in compliance with the temperature limits, even if some of the units were outside the refrigerator in the thermal boxes for up to 660 minutes. This may be important since freezing conditions may cause significant hemolysis and subsequent harm to the patients, and higher temperatures may cause bacterial overgrowth and compromise product quality (222, 223). Further, past reports have suggested significant hemolysis of red cells following helicopter transport, potentially causing fatal outcomes for the transfused patient (224). We did not find any signs of hemolysis. The hemolysis grade was < 0.8% of the total red blood cell mass, within the EU requirements. These findings are supported by more recent reports on helicopter transport of PRBC (225). When comparing LTOWB stored in the blood bank and LTOWB stored forward, there were differences in how the hemoglobin levels had changed at 21 days of storage and the metabolic surrogates. The differences in how the metabolic surrogates changed (pH, lactate, glucose, and BE) probably reflect alterations in gas exchange conditions during storage in the airtight thermal boxes for forward stored blood. However, looking at the absolute values, the clinical impact of these changes is probably without clinical significance. When assessing the hemostatic capacity of LTOWB, we observed that the TEG angle and maximal amplitude had declined less in the forward stored blood during the storage period. We found no differences in platelet count and fibrinogen levels at day one, nor any differences in how these variables changed

during storage. Finally, there were no significant differences in platelet function measured by LTA or flow cytometry. Hence, it seems unlikely that PLT and fibrinogen levels caused the differences in angle and maximal amplitude. Either way, the changes favored forward storage.

As demonstrated with impedance and optical aggregometry, PLT aggregation deteriorates after eight days of storage. This is consistent with previous studies (180). However, our data show that the general viscoelastic hemostatic capacity of cold-stored LTOWB is, to a great extent, maintained for up to 21 days of storage. This is important because it indicates the CWB PLT's ability to catalyze clot formation and contraction throughout the storage period. Standard room temperature stored platelets have previously been shown to suffer from a significant storage lesion with a rapid decline in aggregation function in about 72 hours (161, 162). One explanation for our findings may be the effect of cold storage and the possible resulting bioenergetic conservation of the platelet fraction in CWB (226). The findings support extending storage in environments with limited resources or reducing waste.

As reported in the survey, LTOWB is a preferred option for prehospital services. One reason is reported to be the ability to deliver functional platelets on scene, which may be vital for hemostasis if given early (paper III)(101). In addition, the medical directors highlight the appealing logistics of resuscitation with cold stored LTOWB, specifically a larger volume in each bag and the limited need for transfusing several bags with components (III). Similar to other time-sensitive interventions like early coronary revascularization of myocardial infarction or stroke and early administration of antibiotics in severe sepsis, early hemostatic resuscitation in non-compressible hemorrhage is important. Prehospital care is characterized by a lack of personnel, time-critical interventions, a goal to reduce on-scene times, constrained spaces, and en-route care. These are important factors

that underscore that speed and ease of use are important factors when deciding the prehospital transfusion strategy.

Furthermore, it is well known that avoidance of stress, limiting the task load, and reducing task interruptions may improve patient care. In this context, LTOWB should be evaluated further to quantify changes in prehospital care team task saturation and stress (227, 228, 229).

However, the aforementioned relative lack of prospective data and the cost-benefit considerations in services with few annual transfusions resulting in blood waste seem to represent the major concerns with the implementation of prehospital LTOWB programs (III). From the blood bank perspective, the additional concerns with the lack of possible LTOWB donors play a role. Donor availability is affected by the local policies regarding the definition of low-titer, the potential use of both male and female donors, and whether or not to utilize Rh-positive donors or not (III). Finally, in-hospital utilization of LTOWB for the initial resuscitation of bleeding patients may reduce waste significantly (III). In this respect, prehospital transfusion programs are and should continue to be interlinked with in-hospital strategies to optimize the continuum of care and utilization of blood.

As outlined earlier, most exsanguination deaths occur early but within the realm of EMS care. Our results substantiate this statement, as most deaths occur within 6 hours of injury (paper IV). Although the clinical benefit of prehospital blood transfusions on long-term outcomes is debated, the majority of data shows improvement in short-term outcomes as more patients are admitted to the hospital alive (137, 230, 231). This possible «delayed death effect» is interesting because hospitals receive patients *in extremis* that may need a different approach. As such, changes in prehospital care warrant a shift in in-house strategies as well. Overall, we found that two of three patients receiving transfusions survived the first 24 hours, and only one of two survived beyond 30 days. No cardiac arrest victims survived beyond 24 hours.

Our data from the HEMS service in Norway demonstrate a transfusion rate of 1.4% of all patients (paper IV). This may be considered a restrictive transfusion policy compared to other services, such as the UK EMS services, with a transfusion rate of 3-5.2%(132, 230). Patient demographics in Norway are similar to data from Finland, where the predominant injury pattern was blunt force trauma in middle-aged male patients (16, 232). Additionally, it is worth noting that a significant portion of transfused patients in our study presented with hemorrhagic shock unrelated to trauma. As such, our data is not comparable to the demographic data from the US, where patients present more frequently with penetrating trauma mechanisms. However, our data are more consistent with data from other Scandinavian countries (15, 16, 137). Hence, these findings support that it is difficult to compare data from Europe and the US, even data within Europe, as it may be confounded by the transfusion policies, time to intervention, blood product utilized, patient demographics, and injury patterns amongst trauma victims.

In addition, other interventions made on scene may confound the data. For instance, the overall attitude toward advanced airway management and subsequent on-scene times may impact outcome parameters. Only 29% received prehospital intubation in our study (paper IV). In contrast, US and UK data show intubation rates in excess of 50% (134, 233). This may be important as drug-assisted rapid sequence induction and positive pressure ventilation may delay definitive hemorrhage control and may have a detrimental effect on venous return in patients already in shock (115, 234, 235, 236, 237). As such, knowledge of whether, when, and how to intubate these patients may be crucial for outcome.

Our data demonstrated no logistical issues or adverse events related to the storage, handling, or transfusion of LTOWB.

As outlined, the principles of RDCR mandate early balanced resuscitation for patients in hemorrhagic shock. However, the evidence for prehospital blood transfusion is still debated due to conflicting results in recent prospective

randomized trials. The RePHILL trial found no benefit of PRBC and lyophilized plasma compared to 0.9% saline on outcomes in severely injured trauma patients (132). The PAMPer trial showed significantly lower 30-day mortality in patients who received two units of plasma followed by standard of care compared to standard of care, which could be either crystalloid or crystalloid and PRBC (134). The COMBAT trial found no difference in 28-day mortality between the plasma and crystalloid groups (133). Although several aspects of these trials differ, one of the interesting factors is the difference in the time of entry into the study and, therefore, the timing of interventions. In the COMBAT trial, the total prehospital time was extremely short (mostly less than 20 minutes), perhaps too short to identify potential benefits in the limited population. Indeed, a pooled analysis of PAMPer and COMBAT identified a survival advantage for patients receiving plasma followed by standard of care when the prehospital time was longer than 20 minutes (136). In the RePHILL trial, the time to intervention was 56 minutes from emergency dispatch. As such, the timing of the intervention was maybe too late, and survivors may have survived regardless of the intervention. In the PAMPer trial, total prehospital time was around 40 minutes which is more in line with the golden hour policy. In addition, the retrospective data from Shackelford et al. underscore the importance of early resuscitation to show the benefit of prehospital transfusion (130).

5.3. Limitations

Several limitations of this work have been presented in the specific papers and discussed in the methodological considerations (I-IV).

About emergency intraosseous access as an option for the immediate resuscitation of hemorrhagic shock, it is important to realize that PRBC is extensively used in EMS services today. Although our findings are encouraging with regard to WFWB transfusion, the storage, and refrigeration of other blood

products, such as CWB or PRBC, may potentially affect the red cell membrane integrity. In this regard, fresh autologous whole blood, as used in this study design, may not be a perfect surrogate for the products utilized in civilian clinical practice. As such, we cannot rule out hemolysis following intraosseous transfusion of other blood products (238). Furthermore, the relatively short observation period limits the ability to rule out delayed hemolysis. Concerning this matter, we should have considered a third observation point after 6 hours. However, we would likely have lost subjects to follow up. Also, the hypothesis of hemolysis following IO transfusion is based upon the immediate mechanical lysis due to shearing forces, so the possibility of late hemolysis seems unlikely. It is also important to acknowledge that the study design did not reflect the events following massive transfusion, as only one unit of WFWB was transfused. It may, however, reflect the immediate prehospital care of patients suffering from hemorrhagic shock, as short transport times and limited resources exclude the option of large-volume transfusions. Further, only the sternal access was evaluated. Prospective studies are warranted for both the tibial and humeral IO access sites commonly used worldwide, but there are ethical considerations with the pain associated with transfusion at these sites. Finally, other hypothetical complications, such as fat embolism syndrome, venous thrombosis, and osteonecrosis, which may take up to 48 hours to develop, were not investigated. Magnetic resonance imaging would give further insights into the safety of the intervention. However, we have not received any reports on delayed adverse events.

With regard to forward storage of LTOWB, unfortunately, we could not randomize the units stored forward and the units stored in the blood bank due to the scheduled blood collection of HEMS LTOWB and the available resources at the blood collection facility and the lab. We had to collect the units for the different arms at different time points. This may have caused potential confounders if the characteristics of donors differ from day to day. Therefore, the statistical design was chosen to account for differences at baseline.

One of the strengths of the survey (paper III) was the high response rate. However, there was uncertainty regarding the exact number of transfusion episodes given from 7 of the 20 bases due to underreporting of data in the electronic patient journal systems.

Initially, study IV aimed to collect data from all HEMS services in Norway, but we experienced difficulties with missing data and adherence to the protocol. However, local data was more consistent and robust. As such, paper IV reflects the implementation of LTOWB and hemostatic resuscitation at a single HEMS base. As expected in the prehospital environment, we experienced difficulties with patient follow-up and data gathering. It is difficult to gather reliable data in pre-hospital time-critical emergencies. In addition, some patients are difficult to identify at an early stage, and due to the severity of their injuries makes it difficult to obtain consent. Regarding the potential transfusion reactions, we recognize that this is a topic that is difficult to address in this patient group. Due to overlapping symptoms, it is extremely difficult to recognize an adverse transfusion reaction in patients suffering from hemorrhagic shock due to the clinical condition. Unfortunately, 16 patients declined to provide consent. However, these patients did not differ significantly from the included patients regarding demographics and mechanism of injury/illness. However, there might be a confounding selection bias in the results.

6. Conclusions

6.1. Paper I

WFWB transfusion through the IO route is safe, reliable and provides sufficient flow for the initial resuscitation of hemorrhagic shock

6.2. Paper II

Storage of LTOWB in thermal containers in a pre-hospital HEMS service is feasible and safe. Product quality complies with EU policies for up to 21 days of storage, and hemostatic properties are similar to LTOWB stored in the blood bank. PLT function deteriorates after eight days of storage but remains detectable for up to 21 days. The overall coagulation properties are adequate for up to 21 days.

6.3. Paper III

HEMS services and blood banks report favorable experiences implementing and utilizing LTOWB in Norway. Most HEMS services in Norway want to evaluate the implementation of WB in the future.

6.4. Paper IV

Implementation of a LTOWB program in civilian HEMS is feasible and safe. The logistics of LTOWB transfusion for critical patients in hemorrhagic shock are manageable.

7. Further perspectives

This thesis has contributed with knowledge regarding the prehospital implementation of LTOWB. Although many EMS systems have implemented WB or BCT for the initial hemostatic resuscitation of hemorrhagic shock, the benefit of early prehospital blood transfusion is still debated. As stated in Paper IV, there is a need to further investigate the efficacy of prehospital LTOWB transfusion in prospective trials. There are different attitudes and opinions on the use of LTOWB, which in part could be explained by the absence of robust scientific evidence for or against prehospital LTOWB transfusions, leaving space for opinion-based approaches. The different attitudes seem to be driven by individual views and experiences, differences in regulations, and the regional availability of potential donors. Regarding hard endpoints, today, there is yet not enough clinical evidence to support or refute the clinical superiority of LTOWB in RDCR compared to BCT. With this in mind, we are now awaiting a multitude of results from prospective trials. To mention a few, the French are conducting the STORHM study (Sang Total pour la Reanimation des Hemorrhagies Massive, Clinical Trials NCT04431999) comparing LTOWB to 1:1:1 fixed ratio BCT in massive traumatic hemorrhage. The U.S. S.W.A.T. trial (Shock, Whole Blood, and assessment of TBI, Clinical Trials NCT03402035) is a four-year, multicenter, prospective observational cohort study that compares LTOWB to BCT. The U.K. SWIFT trial (ISRCTN23657907) compares pre-hospital LTOWB to PRBC and plasma transfusions.

Moreover, the timing and triggers of the different RDCR interventions, as well as further knowledge on which patient may benefit, is of interest. Although some retrospective evidence from the military population suggests that blood transfusion should be initiated early to be beneficial, it is still unclear what the optimal timing for pre-hospital blood transfusion in civilian trauma and non-

trauma victims is. Although most will agree that a patient in hemorrhagic shock benefits from an early blood transfusion, the transfusion triggers need to be established. At last, there is a need to develop diagnostic tools that can help providers identify patients on the verge of shock to secure early intervention. It is important to call attention to the fact that it is difficult to generalize conclusions from prospective randomized data and extremely hard to conduct prospective trials due to the limited population, challenging research environment, the heterogeneity of conditions and trauma systems, as well as the numerous potential confounders in these complex patient pathways. The patient demographics, injury patterns, pre-hospital provider experience, on-scene times, and pre-hospital treatment algorithms may differ. Even the composition of the blood components may vary in the different transfusion programs. As such, it is essential to recognize that even retrospective data is of great value in this field - especially if interpreted along known physiologic principles.

We are aiming to further investigate the logistical burden of on-scene RDCR. As interventions are limited by the inherent environmental challenges in pre-hospital care, there should be opportunities in the bundle of care for patients in Hemorrhagic shock.

Ideally, tomorrow's pre-hospital transfusion will be administered timely, based on criteria specific for hemorrhagic shock, to the patient who benefits, without delay in definitive care at the hospital.

8. References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015;386(9995):743-800.
3. Folkehelseinstituttet. FHI Statistikkbank 2022 [updated 26.09.2022. Available from: https://statistikk.fhi.no/dar/alle-dodsfall?dodsfallEtter=Årsak&dodsfallFordeltPaa=Tidsrom&avsnitt=19.1,19.2,19.3,19.4&diagramtype=tabell&tidsrom=2021,2021.
4. Finkelstein E, Corso PS, Miller TR. The incidence and economic burden of injuries in the United States: Oxford University Press, USA; 2006.
5. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. Sci Am. 1983;249(2):28-35.
6. Bardes JM, Inaba K, Schellenberg M, Grabo D, Strumwasser A, Matsushima K, et al. The contemporary timing of trauma deaths. Journal of Trauma and Acute Care Surgery. 2018;84(6):893-9.
7. McNicholl BP. The golden hour and prehospital trauma care. Injury. 1994;25(4):251-4.
8. Pfeifer R, Tarkin IS, Rocos B, Pape H-C. Patterns of mortality and causes of death in polytrauma patients—Has anything changed? Injury. 2009;40(9):907-11.
9. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127-36.
10. Davis JS, Satahoo SS, Butler FK, Dermer H, Naranjo D, Julien K, et al. An analysis of prehospital deaths: Who can we save? J Trauma Acute Care Surg. 2014;77(2):213-8.
11. Kotwal RS, Howard JT, Orman JA, Tarpey BW, Bailey JA, Champion HR, et al. The Effect of a Golden Hour Policy on the Morbidity and Mortality of Combat Casualties. JAMA Surg. 2016;151(1):15-24.
12. Houghton AC, Friedman JK, Smith AA, Toraih EA, Flanagan MR, Schroll RW, et al. Zero Preventable Deaths by 2020: Analysis of

Prehospital and Emergency Department Deaths Following Penetrating Trauma Stratified by Anatomic Location. Am Surg. 2021;87(5):784-9.
13. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. J Trauma Acute Care Surg. 2012;73(6 Suppl 5):S431-7.
14. Holler JG, Bech CN, Henriksen DP, Mikkelsen S, Pedersen C, Lassen AT. Nontraumatic hypotension and shock in the emergency department and the prehospital setting, prevalence, etiology, and mortality: a systematic review. PLoS One. 2015;10(3):e0119331.
15. Thiels CA, Aho JM, Fahy AS, Parker ME, Glasgow AE, Berns KS, et al. Prehospital Blood Transfusions in Non-Trauma Patients. World J Surg. 2016;40(10):2297-304.
16. Angerman S, Kirves H, Nurmi J. Characteristics of Nontrauma Patients Receiving Prehospital Blood Transfusion with the Same Triggers as Trauma Patients: A Retrospective Observational Cohort Study. Prehosp Emerg Care. 2022;26(2):263-71.
17. Moore W. Medical Classics The Edwin Smith papyrus. British Medical Journal. 2011;342.
18. Homer, Green P. The Iliad. Oakland, California: University of California Press; 2015.
19. Goss CM, Chodkowski EG. Whether blood is contained in the arteries of the living animal by Galen of Pergamon: a translation. Anat Rec. 1985;213(1):1-6.
20. Carty JA, Willis R. On the motion of the heart and blood in animals : a new edition of William Harvey's Exercitatio anatomica de motu cordis et sanguinis in animalibus. Eugene, Oregon: Resource Publications; 2016.
21. Giangrande PL. The history of blood transfusion. Br J Haematol. 2000;110(4):758-67.
22. Zimmerman LM, Howell KM. History of Blood Transfusion. Ann Med Hist. 1932;4(5):415-33.
23. Blundell. Observations on Transfusion of Blood. The Lancet. 1829;12(302):321-4.
24. Millham FH. A brief history of shock. Surgery. 2010;148(5):1026-37.
25. Hardaway RM. Wound Shock: A History of Its Study and Treatment by Military Surgeons. Mil Med. 2004;169(7):iv.
26. Santy P, Moulinier M, Marquis D. Du shock traumatique dans les blessures de guerre: I. De la distinction dans les états de shock chez les grands blessés, du shock nerveux, hémorragique ou infectieux; II. Du role joué par 1'hémorragiedans l'apparition du shock traumatique; III. Analyses d'observation. Bull Mem Soc Chir Paris. 1918;44:205-20.
27. Landsteiner K. On agglutination of normal human blood. Transfusion. 1961;1(1):5-8.

28. Lindeman E. Blood Transfusion by the Syringe Cannula System. Journal of the American Medical Association. 1914;LXIII(18):1542-5.
29. Cusimano R, Cusimano M, Cusimano S. The genius of Alexis Carrel. Can Med Assoc J. 1984;131(9):1142-50.
30. Nathoo N, Lautzenheiser FK, Barnett GH. The first direct human blood transfusion: the forgotten legacy of George W. Crile. Neurosurgery. 2009;64(3 Suppl):ons20-6; discussion ons6-7.
31. Robertson LB. The Transfusion of Whole Blood: A Suggestion for Its More Frequent Employment in War Surgery. Br Med J. 1916;2(2897):38-40.
32. Hess JR, Schmidt PJ. The first blood banker: Oswald Hope Robertson. Transfusion. 2000;40(1):110-3.
33. Stansbury LG, Hess JR. Blood transfusion in World War I: the roles of Lawrence Bruce Robertson and Oswald Hope Robertson in the "most important medical advance of the war". Transfus Med Rev. 2009;23(3):232-6.
34. Blalock A. Shock and Hemorrhage. Bull N Y Acad Med. 1936;12(11):610-22.
35. USA MD. The Physiologic Effects of Wounds, Surgery in World War II (Medical Department, United States Army). 1952.
36. Coates J. Blood Program in World War II: Office of the Surgeon General, Department of the Army; 1989.
37. Kendrick DB, Heaton LD, Coates JB, McFetridge EM, Department USAM. Blood Program in World War II: Supplemented by Experiences in the Korean War: Office of the Surgeon General, Department of the Army; 1989.
38. Tocantins LM, O'Neill J F, Price AH. Infusions of Blood and Other Fluids Via the Bone Marrow in Traumatic Shock and Other Forms of Peripheral Circulatory Failure. Ann Surg. 1941;114(6):1085-92.
39. Doud EA. Massive Intramedullary Infusions. Journal of the American Medical Association. 1942;120(15):1212-3.
40. Papper EM. The Bone Marrow Route for Injecting Fluids and Drugs into the General Circulation. Anesthesiology. 1942;3(3):307-13.
41. Steer A, Hullinghorst RL, Mason RP. The blood program in the Korean War. Mil Med. 1955;117(5):415-26.
42. Ballas M, Nordstrom E. Severe hemolysis following transfusion of one unit of O negative blood. USARV Med Bull. 1968;40(11):50-1.
43. Shires T, Coln D, Carrico J, Lightfoot S. Fluid Therapy in Hemorrhagic Shock. Arch Surg. 1964;88(4):688-93.
44. Carrico CJ, Canizaro PC, Shires GT. Fluid resuscitation following injury: rationale for the use of balanced salt solutions. Crit Care Med. 1976;4(2):46-54.

45. Fishman AP. Shock lung: a distinctive nonentity. Circulation. 1973;47(5):921-3.
46. Hirsch EF, Fletcher JR, Moquin R, Dostalek R, Lucas S. Coagulation changes after combat trauma and sepsis. Surg Gynecol Obstet. 1971;133(3):393-6.
47. McNamara JJ, Burran EL, Stremple JF, Molot MD. Coagulopathy after major combat injury: occurrence, management, and pathophysiology. Ann Surg. 1972;176(2):243-6.
48. Cotton BA, Guy JS, Morris JA, Jr., Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006;26(2):115-21.
49. Bickell WH, Wall MJ, Jr., Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331(17):1105-9.
50. Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, et al. Fresh Whole Blood Transfusions in Coalition Military, Foreign National, and Enemy Combatant Patients During Operation Iraqi Freedom at a U.S. Combat Support Hospital. 2007.
51. Rotondo MF, Schwab CW, McGonigal MD, Phillips GR, 3rd, Fruchterman TM, Kauder DR, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma. 1993;35(3):375-82; discussion 82-3.
52. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma. 2007;62(2):307-10.
53. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63(4):805-13.
54. Perkins JG, Cap AP, Spinella PC, Blackbourne LH, Grathwohl KW, Repine TB, et al. An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. J Trauma. 2009;66(4 Suppl):S77-84; discussion S-5.
55. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471-82.
56. Carmichael SP, 2nd, Lin N, Evangelista ME, Holcomb JB. The Story of Blood for Shock Resuscitation: How the Pendulum Swings. J Am Coll Surg. 2021;233(5):644-53.
57. Barbee RW, Reynolds PS, Ward KR. Assessing shock resuscitation strategies by oxygen debt repayment. Shock. 2010;33(2):113-22.

58. Chaudry IH. Cellular mechanisms in shock and ischemia and their correction. Am J Physiol. 1983;245(2):R117-34.
59. Dunn JO, Mythen MG, Grocott MP. Physiology of oxygen transport. BJA Education. 2016;16(10):341-8.
60. Shoemaker WC, Appel PL, Kram HB. Tissue Oxygen Debt as a Determinant of Lethal and Nonlethal Postoperative Organ Failure. Crit Care Med. 1988;16(11):1117-20.
61. Dunham CM, Siegel JH, Weireter L, Fabian M, Goodarzi S, Guadalupi P, et al. Oxygen debt and metabolic acidemia as quantitative predictors of mortality and the severity of the ischemic insult in hemorrhagic shock. [Baltimore, MD] :1991. p. 231-43.
62. Rixen D, Siegel JH. Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. Crit Care. 2005;9(5):441-53.
63. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010;464(7285):104-7.
64. Santucci R, Sinibaldi F, Cozza P, Polticelli F, Fiorucci L. Cytochrome c: An extreme multifunctional protein with a key role in cell fate. Int J Biol Macromol. 2019;136:1237-46.
65. Weidinger A, Kozlov AV. Biological Activities of Reactive Oxygen and Nitrogen Species: Oxidative Stress versus Signal Transduction. Biomolecules. 2015;5(2):472-84.
66. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44-84.
67. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet. 1999;354(9177):505-8.
68. Johansson PI, Henriksen HH, Stensballe J, Gybel-Brask M, Cardenas JC, Baer LA, et al. Traumatic Endotheliopathy: A Prospective Observational Study of 424 Severely Injured Patients. Ann Surg. 2017;265(3):597-603.
69. Johansson PI, Stensballe J, Ostrowski SR. Shock induced endotheliopathy (SHINE) in acute critical illness - a unifying pathophysiologic mechanism. Crit Care. 2017;21(1):25.
70. Lopez Garcia de Lomana A, Vilhjalmsson AI, McGarrity S, Sigurethardottir R, Anuforo O, Viktorsdottir AR, et al. Metabolic Response in Endothelial Cells to Catecholamine Stimulation Associated with Increased Vascular Permeability. Int J Mol Sci. 2022;23(6).
71. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 11th ed. Philadelphia: Elsevier Saunders; 2011.
72. Siegel JH, Fabian M, Smith JA, Kingston EP, Steele KA, Wells MR, et al. Oxygen debt criteria quantify the effectiveness of early partial

resuscitation after hypovolemic hemorrhagic shock. J Trauma. 2003;54(5):862-80; discussion 80.
73. Ward KR, Ivatury RR, Barbee RW. Endpoints of resuscitation for the victim of trauma. Journal of Intensive Care Medicine. 2001;16(2):55-75.
74. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54(6):1127-30.
75. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma. 2003;55(1):39-44.
76. Doyle D. William Hewson (1739-74): the father of haematology. Br J Haematol. 2006;133(4):375-81.
77. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370(9):847-59.
78. Dickneite G, Doerr B, Kaspereit F. Characterization of the coagulation deficit in porcine dilutional coagulopathy and substitution with a prothrombin complex concentrate. Anesth Analg. 2008;106(4):1070-7, table of contents.
79. Meng ZH, Wolberg AS, Monroe DM, 3rd, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma. 2003;55(5):886-91.
80. Martini WZ, Holcomb JB. Acidosis and coagulopathy: the differential effects on fibrinogen synthesis and breakdown in pigs. Ann Surg. 2007;246(5):831-5.
81. Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. Br J Anaesth. 2010;105(2):116-21.
82. Davenport R, Brohi K. Fibrinogen depletion in trauma: early, easy to estimate and central to trauma-induced coagulopathy. Crit Care. 2013;17(5):190.
83. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg. 2007;245(5):812-8.
84. Campbell JE, Meledeo MA, Cap AP. Comparative response of platelet fV and plasma fV to activated protein C and relevance to a model of acute traumatic coagulopathy. PLoS One. 2014;9(6):e99181.
85. Lijnen HR. Pleiotropic functions of plasminogen activator inhibitor-1. J Thromb Haemost. 2005;3(1):35-45.
86. Griffin JH, Fernandez JA, Gale AJ, Mosnier LO. Activated protein C. J Thromb Haemost. 2007;5 Suppl 1:73-80.
87. Cap A, Hunt BJ. The pathogenesis of traumatic coagulopathy. Anaesthesia. 2015;70 Suppl 1:96-101, e32-4.
88. Gando S, Mayumi T, Ukai T. Activated protein C plays no major roles in the inhibition of coagulation or increased fibrinolysis in acute

coagulopathy of trauma-shock: a systematic review. Thromb J. 2018;16:13.
89. Meledeo MA, Herzig MC, Bynum JA, Wu X, Ramasubramanian AK, Darlington DN, et al. Acute traumatic coagulopathy: The elephant in a room of blind scientists. J Trauma Acute Care Surg. 2017;82(6S Suppl 1):S33-S40.
90. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost. 2007;5(2):266-73.
91. Cryostat 2 Trial 2023 [Available from: https://cryostat2.co.uk.
92. Valeri CR, Khuri S, Ragno G. Nonsurgical bleeding diathesis in anemic thrombocytopenic patients: role of temperature, red blood cells, platelets, and plasma-clotting proteins. Transfusion. 2007;47(4 Suppl):206S-48S.
93. Spann AP, Campbell JE, Fitzgibbon SR, Rodriguez A, Cap AP, Blackbourne LH, et al. The Effect of Hematocrit on Platelet Adhesion: Experiments and Simulations. Biophys J. 2016;111(3):577-88.
94. Eugster M, Reinhart WH. The influence of the haematocrit on primary haemostasis in vitro. Thromb Haemost. 2005;94(6):1213-8.
95. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23-32.
96. Chapman MP, Moore EE, Moore HB, Gonzalez E, Gamboni F, Chandler JG, et al. Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. J Trauma Acute Care Surg. 2016;80(1):16-23; discussion -5.
97. Raza I, Davenport R, Rourke C, Platton S, Manson J, Spoors C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost. 2013;11(2):307-14.
98. Kutcher ME, Redick BJ, McCreery RC, Crane IM, Greenberg MD, Cachola LM, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg. 2012;73(1):13-9.
99. Kleinveld DJB, van Amstel RBE, Wirtz MR, Geeraedts LMG, Goslings JC, Hollmann MW, et al. Platelet-to-red blood cell ratio and mortality in bleeding trauma patients: A systematic review and meta-analysis. Transfusion. 2021;61 Suppl 1(Suppl 1):S243-S51.
100. Dorken Gallastegi A, Naar L, Gaitanidis A, Gebran A, Nederpelt CJ, Parks JJ, et al. Do not forget the platelets: The independent impact of red blood cell to platelet ratio on mortality in massively transfused trauma patients. J Trauma Acute Care Surg. 2022;93(1):21-9.
101. Cardenas JC, Zhang X, Fox EE, Cotton BA, Hess JR, Schreiber MA, et al. Platelet transfusions improve hemostasis and survival in a substudy of

the prospective, randomized PROPPR trial. Blood Adv. 2018;2(14):1696-704.
102. Darlington DN, Wu X, Keesee JD, Cap AP. Severe Trauma and Hemorrhage Leads to Platelet Dysfunction and Changes in Cyclic Nucleotides in The Rat. Shock. 2020;53(4):468-75.
103. Vulliamy P, Kornblith LZ, Kutcher ME, Cohen MJ, Brohi K, Neal MD. Alterations in platelet behavior after major trauma: adaptive or maladaptive? Platelets. 2021;32(3):295-304.
104. Jaffe EA. Cell biology of endothelial cells. Hum Pathol. 1987;18(3):234-9.
105. Aird WC. Endothelium as an organ system. Crit Care Med. 2004;32(5 Suppl):S271-9.
106. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. Ann Surg. 2011;254(2):194-200.
107. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. High circulating adrenaline levels at admission predict increased mortality after trauma. J Trauma Acute Care Surg. 2012;72(2):428-36.
108. Ostrowski SR, Johansson PI. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. J Trauma Acute Care Surg. 2012;73(1):60-6.
109. Selby R. "TEG talk": expanding clinical roles for thromboelastography and rotational thromboelastometry. Hematology Am Soc Hematol Educ Program. 2020;2020(1):67-75.
110. Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. Vasc Health Risk Manag. 2015;11:133-48.
111. Brill JB, Brenner M, Duchesne J, Roberts D, Ferrada P, Horer T, et al. The Role of TEG and ROTEM in Damage Control Resuscitation. Shock. 2021;56(1S):52-61.
112. Bjerkvig CK, Strandenes G, Eliassen HS, Spinella PC, Fosse TK, Cap AP, et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion. 2016;56 Suppl 2(S2):S182-9.
113. White NJ, Ward KR, Pati S, Strandenes G, Cap AP. Hemorrhagic blood failure: Oxygen debt, coagulopathy, and endothelial damage. J Trauma Acute Care Surg. 2017;82(6S Suppl 1):S41-S9.
114. Jenkins DH, Rappold JF, Badloe JF, Berseus O, Blackbourne L, Brohi KH, et al. Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: definitions, current practice, and knowledge gaps. Shock. 2014;41 Suppl 1(Supplement 1):3-12.

115. Hudson AJ, Strandenes G, Bjerkvig CK, Svanevik M, Glassberg E. Airway and ventilation management strategies for hemorrhagic shock. To tube, or not to tube, that is the question! J Trauma Acute Care Surg. 2018;84(6S Suppl 1):S77-S82.
116. Fields JM, Piela NE, Au AK, Ku BS. Risk factors associated with difficult venous access in adult ED patients. Am J Emerg Med. 2014;32(10):1179-82.
117. Armenteros-Yeguas V, Garate-Echenique L, Tomas-Lopez MA, Cristobal-Dominguez E, Moreno-de Gusmao B, Miranda-Serrano E, et al. Prevalence of difficult venous access and associated risk factors in highly complex hospitalised patients. J Clin Nurs. 2017;26(23-24):4267-75.
118. Engels PT, Passos E, Beckett AN, Doyle JD, Tien HC. IV access in bleeding trauma patients: a performance review. Injury. 2014;45(1):77-82.
119. Ferrada P, Callcut RA, Skarupa DJ, Duane TM, Garcia A, Inaba K, et al. Circulation first - the time has come to question the sequencing of care in the ABCs of trauma; an American Association for the Surgery of Trauma multicenter trial. World J Emerg Surg. 2018;13(1):8.
120. Army US. Tactical Combat Casualty Care Handbook, Version 5: Lulu.com; 2020.
121. Connelly CR, Schreiber MA. Endpoints in resuscitation. Curr Opin Crit Care. 2015;21(6):512-9.
122. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011;70(3):652-63.
123. Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D. A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. Health Technol Assess. 2000;4(31):1-57.
124. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma. 2002;52(6):1141-6.
125. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Holcomb JB, Ware DN, et al. Secondary abdominal compartment syndrome is an elusive early complication of traumatic shock resuscitation. Am J Surg. 2002;184(6):538-43; discussion 43-4.
126. Robinson BRH, Cohen MJ, Holcomb JB, Pritts TA, Gomaa D, Fox EE, et al. Risk Factors for the Development of Acute Respiratory Distress Syndrome Following Hemorrhage. Shock. 2018;50(3):258-64.
127. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. American Journal of Surgery. 2003;185(5):485-91.

128. Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. Injury. 2012;43(1):26-32.
129. Eidstuen SC, Uleberg O, Vangberg G, Skogvoll E. When do trauma patients lose temperature? - a prospective observational study. Acta Anaesthesiol Scand. 2018;62(3):384-93.
130. Shackelford SA, Del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, et al. Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival. JAMA. 2017;318(16):1581-91.
131. Rijnhout TWH, Wever KE, Marinus R, Hoogerwerf N, Geeraedts LMG, Jr., Tan E. Is prehospital blood transfusion effective and safe in haemorrhagic trauma patients? A systematic review and meta-analysis. Injury. 2019;50(5):1017-27.
132. Crombie N, Doughty HA, Bishop JRB, Desai A, Dixon EF, Hancox JM, et al. Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Haematol. 2022;9(4):e250-e61.
133. Moore HB, Moore EE, Chapman MP, McVaney K, Bryskiewicz G, Blechar R, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. Lancet. 2018;392(10144):283-91.
134. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. N Engl J Med. 2018;379(4):315-26.
135. Guyette FX, Sperry JL, Peitzman AB, Billiar TR, Daley BJ, Miller RS, et al. Prehospital Blood Product and Crystalloid Resuscitation in the Severely Injured Patient: A Secondary Analysis of the Prehospital Air Medical Plasma Trial. Ann Surg. 2021;273(2):358-64.
136. Pusateri AE, Moore EE, Moore HB, Le TD, Guyette FX, Chapman MP, et al. Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes: A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials. JAMA Surg. 2020;155(2):e195085.
137. Braverman MA, Smith A, Pokorny D, Axtman B, Shahan CP, Barry L, et al. Prehospital whole blood reduces early mortality in patients with hemorrhagic shock. Transfusion. 2021;61 Suppl 1(S1):S15-S21.
138. Walsh M, Moore EE, Moore HB, Thomas S, Kwaan HC, Speybroeck J, et al. Whole Blood, Fixed Ratio, or Goal-Directed Blood Component

Therapy for the Initial Resuscitation of Severely Hemorrhaging Trauma Patients: A Narrative Review. J Clin Med. 2021;10(2):320.
139. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23(1):98.
140. Tapia NM, Chang A, Norman M, Welsh F, Scott B, Wall MJ, Jr., et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg. 2013;74(2):378-85; discussion 85-6.
141. Schochl H, Maegele M, Voelckel W. Fixed ratio versus goal-directed therapy in trauma. Curr Opin Anaesthesiol. 2016;29(2):234-44.
142. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Ann Surg. 2016;263(6):1051-9.
143. Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, et al. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. Intensive Care Med. 2021;47(1):49-59.
144. Hazelton JP, Ssentongo AE, Oh JS, Ssentongo P, Seamon MJ, Byrne JP, et al. Use of Cold-Stored Whole Blood is Associated With Improved Mortality in Hemostatic Resuscitation of Major Bleeding: A Multicenter Study. Ann Surg. 2022;276(4):579-88.
145. Shea SM, Staudt AM, Thomas KA, Schuerer D, Mielke JE, Folkerts D, et al. The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage. Transfusion. 2020;60 Suppl 3(S3):S2-S9.
146. Nowadly CD, Fisher AD, Borgman MA, Mdaki KS, Hill RL, Nicholson SE, et al. The Use of Whole Blood Transfusion During Non-Traumatic Resuscitation. Mil Med. 2022;187(7-8):e821-e5.
147. Thies KC, Truhlar A, Keene D, Hinkelbein J, Rutzler K, Brazzi L, et al. Pre-hospital blood transfusion - an ESA survey of European practice. Scand J Trauma Resusc Emerg Med. 2020;28(1):79.
148. Spinella PC, Doctor A. Role of transfused red blood cells for shock and coagulopathy within remote damage control resuscitation. Shock. 2014;41 Suppl 1(Supplement 1):30-4.
149. Obrador R, Musulin S, Hansen B. Red blood cell storage lesion. J Vet Emerg Crit Care (San Antonio). 2015;25(2):187-99.
150. Garcia-Roa M, Del Carmen Vicente-Ayuso M, Bobes AM, Pedraza AC, Gonzalez-Fernandez A, Martin MP, et al. Red blood cell storage time and transfusion: current practice, concerns and future perspectives. Blood Transfus. 2017;15(3):222-31.

151. Kiraly LN, Underwood S, Differding JA, Schreiber MA. Transfusion of aged packed red blood cells results in decreased tissue oxygenation in critically injured trauma patients. J Trauma. 2009;67(1):29-32.
152. Spinella PC, Carroll CL, Staff I, Gross R, Mc Quay J, Keibel L, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. Crit Care. 2009;13(5):R151.
153. Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, et al. Effect of Short-Term vs. Long-Term Blood Storage on Mortality after Transfusion. N Engl J Med. 2016;375(20):1937-45.
154. Jones AR, Patel RP, Marques MB, Donnelly JP, Griffin RL, Pittet JF, et al. Older Blood Is Associated With Increased Mortality and Adverse Events in Massively Transfused Trauma Patients: Secondary Analysis of the PROPPR Trial. Ann Emerg Med. 2019;73(6):650-61.
155. Pusateri AE, Given MB, Schreiber MA, Spinella PC, Pati S, Kozar RA, et al. Dried plasma: state of the science and recent developments. Transfusion. 2016;56 Suppl 2:S128-39.
156. Sunde GA, Vikenes B, Strandenes G, Flo KC, Hervig TA, Kristoffersen EK, et al. Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S26-30.
157. Feuerstein SJ, Skovmand K, Moller AM, Wildgaard K. Freeze-dried plasma in major haemorrhage: a systematic review. Vox Sang. 2020;115(4):263-74.
158. Matijevic N, Wang YW, Cotton BA, Hartwell E, Barbeau JM, Wade CE, et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma Acute Care Surg. 2013;74(1):84-90; discussion -1.
159. Cao Y, Dua A, Matijevic N, Wang YW, Pati S, Wade CE, et al. Never-frozen liquid plasma blocks endothelial permeability as effectively as thawed fresh frozen plasma. J Trauma Acute Care Surg. 2014;77(1):28-33; discussion
160. Meledeo MA, Peltier GC, McIntosh CS, Bynum JA, Corley JB, Cap AP. Coagulation function of never frozen liquid plasma stored for 40 days. Transfusion. 2021;61 Suppl 1(S1):S111-S8.
161. Reddoch KM, Pidcoke HF, Montgomery RK, Fedyk CG, Aden JK, Ramasubramanian AK, et al. Hemostatic function of apheresis platelets stored at 4 degrees C and 22 degrees C. Shock. 2014;41 Suppl 1(0 1):54-61.
162. Kreuger AL, Caram-Deelder C, Jacobse J, Kerkhoffs JL, van der Bom JG, Middelburg RA. Effect of storage time of platelet products on clinical outcomes after transfusion: a systematic review and meta-analyses. Vox Sang. 2017;112(4):291-300.

163. Murphy S, Gardner FH. Effect of storage temperature on maintenance of platelet viability--deleterious effect of refrigerated storage. N Engl J Med. 1969;280(20):1094-8.
164. Hoffmeister KM, Felbinger TW, Falet H, Denis CV, Bergmeier W, Mayadas TN, et al. The clearance mechanism of chilled blood platelets. Cell. 2003;112(1):87-97.
165. Becker GA, Tuccelli M, Kunicki T, Chalos MK, Aster RH. Studies of platelet concentrates stored at 22 C nad 4 C. Transfusion. 1973;13(2):61-8.
166. Strandenes G, Sivertsen J, Bjerkvig CK, Fosse TK, Cap AP, Del Junco DJ, et al. A Pilot Trial of Platelets Stored Cold versus at Room Temperature for Complex Cardiothoracic Surgery. Anesthesiology. 2020;133(6):1173-83.
167. Zielinski MD, Stubbs JR, Berns KS, Glassberg E, Murdock AD, Shinar E, et al. Prehospital blood transfusion programs: Capabilities and lessons learned. J Trauma Acute Care Surg. 2017;82(6S Suppl 1):S70-S8.
168. Taylor AL, Corley JB, Cap AP, Swingholm MT, Nance ET, Gonzales R, et al. The U.S. Armed Services Blood Program support to U.S. Central Command 2014-2021: Transformation of combat trauma resuscitation through blood product innovation and expansion of blood availability far forward. Transfusion. 2022;62 Suppl 1:S167-S76.
169. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma. 2009;66(4 Suppl):S69-76.
170. Strandenes G, Hervig TA, Bjerkvig CK, Steve i, Eliassen HS, Fosse TK, et al. The Lost Art of Whole Blood Transfusion in Austere Environments. 2015.
171. Strandenes G, De Pasquale M, Cap AP, Hervig TA, Kristoffersen EK, Hickey M, et al. Emergency whole-blood use in the field: a simplified protocol for collection and transfusion. Shock. 2014;41 Suppl 1(Supplement 1):76-83.
172. Strandenes G, Sivertsen J, Eliassen H, Braathen H, Hervig TA. Staff officers as blood suppliers: Effects of repeated donations and autologous reinfusions of untransfused units. J Trauma Acute Care Surg. 2018;84(6S Suppl 1):S89-S92.
173. Katsura M, Matsushima K, Kitamura R, Kawasaki K, Takaesu R, Fukuma S, et al. The use of warm fresh whole blood transfusion in the austere setting: A civilian trauma experience. J Trauma Acute Care Surg. 2020;89(3):e28-e33.
174. Apelseth TO, Arsenovic M, Strandenes G. The Norwegian blood preparedness project: A whole blood program including civilian walking blood banks for early treatment of patients with life-threatening bleeding

in municipal health care services, ambulance services, and rural hospitals. Transfusion. 2022;62 Suppl 1(Suppl 1):S22-S9.
175. Eliassen HS, Hervig T, Backlund S, Sivertsen J, Iversen VV, Kristoffersen M, et al. Immediate effects of blood donation on physical and cognitive performance-A randomized controlled double-blinded trial. J Trauma Acute Care Surg. 2018;84(6S Suppl 1):S125-S31.
176. Doughty H, Thompson P, Cap AP, Spinella PC, Glassberg E, Skogrand Eliassen H, et al. A proposed field emergency donor panel questionnaire and triage tool. Transfusion. 2016;56 Suppl 2:S119-27.
177. Hess JR. Resuscitation of trauma-induced coagulopathy. Hematology Am Soc Hematol Educ Program. 2013;2013(1):664-7.
178. Kornblith LZ, Howard BM, Cheung CK, Dayter Y, Pandey S, Busch MP, et al. The whole is greater than the sum of its parts: hemostatic profiles of whole blood variants. J Trauma Acute Care Surg. 2014;77(6):818-27.
179. Nepstad I, Reikvam H, Strandenes G, Hess JR, Apelseth TO, Hervig TA. Comparison of in vitro responses to fresh whole blood and reconstituted whole blood after collagen stimulation. Blood Transfus. 2014;12(1):50-5.
180. Strandenes G, Austlid I, Apelseth TO, Hervig TA, Sommerfelt-Pettersen J, Herzig MC, et al. Coagulation function of stored whole blood is preserved for 14 days in austere conditions: A ROTEM feasibility study during a Norwegian antipiracy mission and comparison to equal ratio reconstituted blood. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S31-8.
181. Cohen T, Haas T, Cushing MM. The strengths and weaknesses of viscoelastic testing compared to traditional coagulation testing. Transfusion. 2020;60 Suppl 6(S6):S21-S8.
182. Tucker H, Green L, Brohi K, Cardigan R, Davenport R, Davies J, et al. Transfusion Strategies in the Pre-Hospital Setting: Evaluating the Logistical Benefits of Pre-Hospital Whole Blood Transfusion, and a National Survey of Pre-Hospital Blood Transfusion 2021 [Available from: https://assets.researchsquare.com/files/rs-148719/v1/04cbcf64-71d2-4f36-a4a6-4a03fabe9ece.pdf?c=1631871756.
183. Tucker H, Brohi K, Tan J, Aylwin C, Bloomer R, Cardigan R, et al. Association of red blood cells and plasma transfusion versus red blood cell transfusion only with survival for treatment of major traumatic hemorrhage in prehospital setting in England: a multicenter study. Crit Care. 2023;27(1):25.
184. Yazer MH, Seheult J, Kleinman S, Sloan SR, Spinella PC. Who's afraid of incompatible plasma? A balanced approach to the safe transfusion of blood products containing ABO-incompatible plasma. Transfusion. 2018;58(2):532-8.

185. Yazer MH, Spinella PC. An international survey on the use of low titer group O whole blood for the resuscitation of civilian trauma patients in 2020. Transfusion. 2020;60 Suppl 3(S3):S176-S9.
186. Troughton M, Young PP. Conservation of Rh negative Low Titer O Whole Blood (LTOWB) and the need for a national conversation to define its use in trauma transfusion protocols. Transfusion. 2021;61(6):1966-71.
187. Seheult JN, Triulzi DJ, Alarcon LH, Sperry JL, Murdock A, Yazer MH. Measurement of haemolysis markers following transfusion of uncrossmatched, low-titre, group O+ whole blood in civilian trauma patients: initial experience at a level 1 trauma centre. Transfus Med. 2017;27(1):30-5.
188. Seheult JN, Bahr M, Anto V, Alarcon LH, Corcos A, Sperry JL, et al. Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients. Transfusion. 2018;58(10):2280-8.
189. Hagen KG, Strandenes G, Kristoffersen EK, Braathen H, Sivertsen J, Bjerkvig CK, et al. A whole blood based resuscitation strategy in civilian medical services: Experience from a Norwegian hospital in the period 2017-2020. Transfusion. 2021;61 Suppl 1(S1):S22-S31.
190. Yazer MH, Corcos A, J LS, Triulzi DJ, Leeper C. Receipt of at least 4 units of low titer group O whole blood with titer <100 does not lead to hemolysis in adult trauma patients. Transfusion. 2022;62 Suppl 1(S1):S72-S9.
191. Bux J. Transfusion-related acute lung injury (TRALI): a serious adverse event of blood transfusion. Vox Sang. 2005;89(1):1-10.
192. Selleng K, Jenichen G, Denker K, Selleng S, Mullejans B, Greinacher A. Emergency transfusion of patients with unknown blood type with blood group O Rhesus D positive red blood cell concentrates: a prospective, single-centre, observational study. Lancet Haematol. 2017;4(5):e218-e24.
193. Yazer MH, Gorospe J, Cap AP. Mixed feelings about mixed-field agglutination: A pathway for managing females of childbearing potential of unknown RhD-type who are transfused RhD-positive and RhD-negative red blood cells during emergency hemorrhage resuscitation. Transfusion. 2021;61 Suppl 1:S326-S32.
194. Yazer MH, Diaz-Valdes JR, Triulzi DJ, Cap AP. Wider perspectives: It's a changing world-The use of ABO-incompatible plasma for resuscitating massively bleeding patients. Br J Haematol. 2022.
195. Saverimuttu J, Greenfield T, Rotenko I, Crozier J, Jalaludin B, Harvey M. Implications for urgent transfusion of uncrossmatched blood in the emergency department: The prevalence of clinically significant red cell antibodies within different patient groups. Emerg Med (Fremantle). 2003;15(3):239-43.

196. Bell MC, Olshaker JS, Brown CK, McNamee GA, Jr., Fauver GM. Intraosseous transfusion in an anesthetized swine model using 51Cr-labeled autologous red blood cells. J Trauma. 1991;31(11):1487-9.
197. Harris M, Balog R, Devries G. What is the evidence of utility for intraosseous blood transfusion in damage-control resuscitation? J Trauma Acute Care Surg. 2013;75(5):904-6.
198. Burgert JM, Mozer J, Williams T, Gegel BT, Johnson S, Bentley M, et al. Effects of intraosseous transfusion of whole blood on hemolysis and transfusion time in a swine model of hemorrhagic shock: a pilot study. AANA J. 2014;82(3):198-202.
199. Krepela A, Auten J, McLean J, Fortner G, Murnan S, Kemp J, et al. 352 A Comparison of Flow Rates and Hematologic Safety Between Intraosseous Blood Transfusion Strategies in a Swine (Sus scrofa) Model of Hemorrhagic Shock: A Pilot Study. Annals of Emergency Medicine. 2017;70(4):S139-S.
200. Auten JD, McEvoy CS, Roszko PJ, Polk TM, Kachur RE, Kemp JD, et al. Safety of Pressurized Intraosseous Blood Infusion Strategies in a Swine Model of Hemorrhagic Shock. J Surg Res. 2020;246:190-9.
201. Klose T, Borchert HH, Pruss A, Roth WK, Bohnen HR, Putzker M. Current concepts for quality assured long-distance transport of temperature-sensitive red blood cell concentrates. Vox Sang. 2010;99(1):44-53.
202. Reiter U, Wagner T, Kozma N, Reiter G, Lanzer G. Core and surface temperatures in a red-blood-cell unit during storage and transport. Vox Sang. 2011;101(1):10-5.
203. Hervig T, Kaada S, Seghatchian J. Storage and handling of blood components - perspectives. Transfus Apher Sci. 2014;51(2):103-6.
204. Guide to the preparation, use and quality assurance of blood components.: European Directorate for the Quality of Medicines: Council of Europe; 2017.
205. Carll T, Wool GD. Basic principles of viscoelastic testing. Transfusion. 2020;60 Suppl 6:S1-S9.
206. Kinard TN, Christie A, Greilich PE, Sarode R. Comparison Of Thromboelastography (TEG) With Rotational Thromboelastrometry (ROTEM) In Surgical Patients. Blood. 2013;122(21):3659.
207. Koltai K, Kesmarky G, Feher G, Tibold A, Toth K. Platelet Aggregometry Testing: Molecular Mechanisms, Techniques and Clinical Implications. Int J Mol Sci. 2017;18(8):1803.
208. Fox SC, May JA, Dovlatova N, Glenn JR, Johnson A, White AE, et al. How does measurement of platelet P-selectin compare with other methods of measuring platelet function as a means of determining the effectiveness of antiplatelet therapy? Platelets. 2019;30(3):290-5.

209. Carr BG, Brachet T, David G, Duseja R, Branas CC. The time cost of prehospital intubation and intravenous access in trauma patients. Prehosp Emerg Care. 2008;12(3):327-32.
210. Cotton BA, Jerome R, Collier BR, Khetarpal S, Holevar M, Tucker B, et al. Guidelines for prehospital fluid resuscitation in the injured patient. J Trauma. 2009;67(2):389-402.
211. Prottengeier J, Albermann M, Heinrich S, Birkholz T, Gall C, Schmidt J. The prehospital intravenous access assessment: a prospective study on intravenous access failure and access delay in prehospital emergency medicine. Eur J Emerg Med. 2016;23(6):442-7.
212. Paxton J. Intraosseous vascular access: A review. Trauma. 2012;14(3):195-232.
213. Simmons CT. Henry Darcy (1803-1858): Immortalised by his scientific legacy. Hydrogeology Journal. 2008;16(6):1023-38.
214. Frascone RJ, Salzman JG, Adams AB, Bliss P, Wewerka SS, Dries DJ. Evaluation of intraosseous pressure in a hypovolemic animal model. J Surg Res. 2015;193(1):383-90.
215. Sunde GA, Heradstveit BE, Vikenes BH, Heltne JK. Emergency intraosseous access in a helicopter emergency medical service: a retrospective study. Scand J Trauma Resusc Emerg Med. 2010;18:52.
216. Savell S, Mora AG, Perez CA, Bebarta VS, Maddry MJ. En route intraosseous access performed in the combat setting. Am J Disaster Med. 2016;11(4):225-31.
217. Tyler JA, Perkins Z, De'Ath HD. Intraosseous access in the resuscitation of trauma patients: a literature review. Eur J Trauma Emerg Surg. 2021;47(1):47-55.
218. Plewa MC, King RW, Fenn-Buderer N, Gretzinger K, Renuart D, Cruz R. Hematologic safety of intraosseous blood transfusion in a swine model of pediatric hemorrhagic hypovolemia. Acad Emerg Med. 1995;2(9):799-809.
219. Savage SA, Sumislawski JJ, Zarzaur BL, Dutton WP, Croce MA, Fabian TC. The new metric to define large-volume hemorrhage: results of a prospective study of the critical administration threshold. J Trauma Acute Care Surg. 2015;78(2):224-9; discussion 9-30.
220. Macnab A, Christenson J, Findlay J, Horwood B, Johnson D, Jones L, et al. A new system for sternal intraosseous infusion in adults. Prehosp Emerg Care. 2000;4(2):173-7.
221. Maher P, Utarnachitt R, Louzon MJ, Gary R, Sen N, Hess JR. Logistical Concerns for Prehospital Blood Product Use by Air Medical Services. Air Med J. 2017;36(5):263-7.
222. Nilsson L, Hedner U, Nilsson IM, Robertson B. Shelf-life of bank blood and stored plasma with special reference to coagulation factors. Transfusion. 1983;23(5):377-81.

223. Brunskill S, Thomas S, Whitmore E, McDonald CP, Doree C, Hopewell S, et al. What is the maximum time that a unit of red blood cells can be safely left out of controlled temperature storage? Transfus Med Rev. 2012;26(3):209-23 e3.
224. Macnab AJ, Pattman B, Wadsworth LD. Potentially fatal hemolysis of cross-matched blood during interfacility transport: standards of practice for safe transport of stored blood products. Air Med J. 1996;15(2):69-72.
225. Otani T, Oki K, Akino M, Tamura S, Naito Y, Homma C, et al. Effects of helicopter transport on red blood cell components. Blood Transfus. 2012;10(1):78-86.
226. Bynum JA, Meledeo MA, Getz TM, Rodriguez AC, Aden JK, Cap AP, et al. Bioenergetic profiling of platelet mitochondria during storage: 4 degrees C storage extends platelet mitochondrial function and viability. Transfusion. 2016;56 Suppl 1:S76-84.
227. Morrison JB, Rudolph JW. Learning from accident and error: avoiding the hazards of workload, stress, and routine interruptions in the emergency department. Acad Emerg Med. 2011;18(12):1246-54.
228. Drews FA. The frequency and impact of task interruptions in the ICU. Proceedings of the Human Factors and Ergonomics Society Annual Meeting. 2016;51(11):683-6.
229. Prottengeier J, Keunecke JG, Gall C, Eiche C, Moritz A, Birkholz T. Single mission workload and influencing factors in German prehospital emergency medicine - a nationwide prospective survey of 1361emergency missions. Scand J Trauma Resusc Emerg Med. 2019;27(1):75.
230. Rehn M, Weaver A, Brohi K, Eshelby S, Green L, Roislien J, et al. Effect of Prehospital Red Blood Cell Transfusion on Mortality and Time of Death in Civilian Trauma Patients. Shock. 2019;51(3):284-8.
231. Gruen DS, Guyette FX, Brown JB, Okonkwo DO, Puccio AM, Campwala IK, et al. Association of Prehospital Plasma With Survival in Patients With Traumatic Brain Injury: A Secondary Analysis of the PAMPer Cluster Randomized Clinical Trial. JAMA Netw Open. 2020;3(10):e2016869.
232. Yliharju H, Jama T, Nordquist H. Initial experiences of prehospital blood product transfusions between 2016 and 2020 in Paijat-Hame hospital district, Finland. Scand J Trauma Resusc Emerg Med. 2022;30(1):39.
233. Lyon RM, de Sausmarez E, McWhirter E, Wareham G, Nelson M, Matthies A, et al. Pre-hospital transfusion of packed red blood cells in 147 patients from a UK helicopter emergency medical service. Scand J Trauma Resusc Emerg Med. 2017;25(1):12.
234. Morgan BC, Martin WE, Hornbein TF, Crawford EW, Guntheroth WG. Hemodynamic effects of intermittent positive pressure respiration. Anesthesiology. 1966;27(5):584-90.

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Cold-stored whole blood in a Norwegian emergency helicopter service: an observational study on storage conditions and product quality

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BACKGROUND: Increasing numbers of emergency medical service agencies and hospitals are developing the capability to administer blood products to patients with hemorrhagic shock. Cold-stored whole blood (WB) is the only single product available to prehospital providers who aim to deliver a balanced resuscitation strategy. However, there are no data on the safety and in vitro characteristics of prehospital stored WB. This study aimed to describe the effects on in vitro quality of storing WB at remote helicopter bases in thermal insulating containers.

STUDY DESIGN AND METHODS: We conducted a two-armed single-center study. Twenty units (test) were stored in airtight thermal insulating containers, and 20 units (controls) were stored according to routine procedures in the Haukeland University Hospital Blood Bank. Storage conditions were continuously monitored during emergency medical services missions and throughout remote and blood bank storage. Hematologic and metabolic variables, viscoelastic properties, and platelet (PLT) aggregation were measured on Days 1, 8, 14, and 21.

RESULTS: Storage conditions complied with the EU guidelines throughout remote and in-hospital storage for 21 days. There were no significant differences in PLT aggregation, viscoelastic properties, and hematology variables between the two groups. Minor significantly lower pH, glucose, and base excess and higher lactate were observed after storage in airtight containers.

CONCLUSION: Forward cold storage of WB is safe and complies with EU standards. No difference is observed in hemostatic properties. Minor differences in metabolic variables may be related to the anaerobic conditions within the thermal box.

ABBREVIATIONS: aPTT = activated partial thromboplastin time; BE = base excess; CWB = cold whole blood; DCR = damage control resuscitation; LTA = light transmission aggregometry; MA = maximum achieved clot strength; HEMS = helicopter emergency medical services; PRP = platelet-rich plasma; TRAP = thrombin receptor-activating peptide; WB = whole blood.

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During the past two decades there has been a paradigm shift in resuscitation strategies for major hemorrhage and hemorrhagic shock.[1–3] Damage control resuscitation (DCR) strategies now favor the early transfusion of blood components containing red blood cells (RBCs), platelets (PLTs), and plasma, contradicting the previous policies favoring the use of clear fluids. Although definitive evidence concerning transfusion ratios is lacking, there is a strong trend to aim for physiologic ratios of blood components in the initial phase of resuscitation. Simultaneously, there is a clear vision that the prehospital phase should be as short as possible even if blood components are available at an early stage.[4–6] Balanced blood product replacement aims at addressing both shock and coagulopathy, which underscores the rationale for starting this approach in the prehospital phase of care. A growing number of prehospital emergency services in Europe and the United States have implemented this strategy.[7] Although DCR principles address trauma, early prehospital transfusion of blood products may also benefit patients who suffer from hemorrhagic shock due to medical conditions.[8] It is also common for helicopter emergency medical services (HEMS) to respond to rural clinics and hospitals with limited transfusion capabilities for stabilization and subsequent transport of bleeding patients. Prehospital transfusion programs may be of value in these circumstances as well.

Owing to the logistics and limitations associated with transfusion in the prehospital arena, DCR based on component therapy may not be feasible. At present, cold-stored RBCs and lyophilized plasma are the components most widely used in the prehospital environment.[9] Hence, the PLT supply is the weak link to achieve what may be considered currently a "gold standard" DCR. In most circumstances it is logistically impossible to supply room temperature–stored agitated PLTs for forward resuscitation. Even if cold-stored PLTs are considered as an alternative, the component-based strategy suffers from the fact that the 1:1:1 ratio yields a dilute mixture because of the RBC additive solutions.[10] Second, it is a great logistic challenge for the prehospital provider to deliver three different products simultaneously in a time-sensitive emergency. Recent experience from the war theaters in Iraq and Afghanistan suggest that whole blood (WB) resuscitation for trauma victims may be a viable option in this context.[11–15]

At present in excess of 30 HEMS in the United States and Norway carry cold-stored low-titer group O WB to patients. Further, several military units have implemented WB in war theaters over the past 6 years.[13,16,17]

The storage conditions for cold WB (CWB) in the prehospital environment differ from in-hospital CWB storage. Prehospital CWB is usually stored in closed isothermal containers. Impaired gas-exchange conditions raise concerns about the potential reduction in hemostatic function due to impaired PLT function in the product.

The problem with adhering to storage standards may be a reason why some emergency medical services no longer carry blood. The lack of data on prehospital storage conditions and data on the hemostatic function of prehospital stored WB is the rationale for conducting this study.[18]

In our study we wanted to assess how forward cold storage of WB in a civilian emergency helicopter service would affect the product quality. Our primary objective was to evaluate if the storage conditions support blood that complies with EU standards for up to 21 days of storage.[19] The secondary objective was to assess product in vitro quality and hemostatic function of WB during storage for up to 21 days in an approved airtight thermal insulating storage container.

MATERIALS AND METHODS

Study design and ethics

This is a prospective single-center, two-armed observational study of forward storage of WB in airtight thermal insulating storage containers. The study was conducted at the Department of Immunology and Transfusion Medicine, Haukeland University Hospital (Bergen, Norway), and at the Norwegian Air Ambulance HEMS base Grønneviksøren (Bergen, Norway), a location 2 km from Haukeland University Hospital, from May to October 2017. According to routine procedures for the Bergen HEMS prehospital blood program, WB units in the test group (HEMS group) were stored continuously in an airtight approved container at the HEMS base for 1 week before being returned to the blood bank for continuous total storage of 21 days in the thermal container. The control group units were stored according to routine procedures without agitation in a temperature-controlled refrigerator at 4 ± 2^{o}C in the blood bank the entire study period. Sampling from the test units was performed immediately before and after transfer to the base. The test units were included in the study from the regular inventory at the HEMS base if not used at the HEMS base within 7 days of storage. There were no patient interventions. The study was approved by the regional ethics committee (REK ID 2017/157). Informed written consent was obtained from all donors of WB.

Bergen HEMS

The emergency helicopter service in Bergen, Norway, responds to both medical and trauma cases in a 60:40 ratio 24 hr/day 365 days/year. The HEMS is staffed with an experienced prehospital anesthesiologist, a HEMS rescue paramedic, and a pilot. Emergency response is carried out by helicopter or by a rapid response car. Bergen HEMS implemented routinely cold-stored, leukoreduced low-titer group O WB for remote hemostatic resuscitation in December 2015. Also, lyophilized plasma is available in the service.

Collection and preparation of WB units

Whole blood was collected from regular blood donors using the 450-mL WB-SP CPD collection set (BB*LGQ456E6, Terumo BCT). The WB units were rested for 2 hours followed by a gravitational filtration through the inline PLT-sparing, leukoreducing filter, allowing for a PLT content of more than 90% of the unit before filtration. The residual white blood cell (WBC) concentration was less than 1×10^6/unit, in line with requirements for cellular blood components. To minimize risk of hemolytic transfusion reactions, all blood donors had blood group O. The titers of IgM anti-A and anti-B were below 256 and all units were correspondingly labeled "low titer." Two CWB units were dispatched to the HEMS service each week.

Cold chain maintenance and forward monitoring

The test group WB units (n = 20) were transferred to an approved primed portable thermal container (Crēdo Duracube HD with Golden Hour inner container, Pelican BioThermal) together with a data logger that recorded ambient temperature, three-axis acceleration, humidity, light, and barometric pressure (MSR 145 mini datalogger, MSR Electronics GMBH). According to local routines, the container was then placed in a regular refrigerator at the HEMS base. The units were carried on missions in the container for 7 days before returned to the Department of Immunology and Transfusion Medicine at Haukeland University Hospital and then stored in the same container for an additional 14 days up to a total of 21 days. The container was only brought on HEMS missions involving calls to patients with potential bleeding. HEMS crew members recorded the duration of the mission and how long the thermal box was outside the refrigerator. These records were compared to the data logger recordings inside the box. Control group WB units (n = 20) were stored without agitation in a conventional approved, monitored refrigerator (2-6°C) in the blood bank according to routine.

Laboratory investigations

Samples were collected on Days 1, 8, 14, and 21 by sterile transfer of approximately 25 mL to a transfer bag (Teruflex, BB*T015CM, Terumo BCT), which was then used to further aliquot to the appropriate sample tubes.

Leukoreduction status was verified by counting residual WBCs using the WBC counting kit and flow cytometer (BD LeucoCount and a FACSCanto II, respectively (BD Biosciences;). Hematologic variables (hemoglobin [Hb], hematocrit [Hct], RBC count, PLT count, and mean PLT volume) were quantified with a hematology analyzer (Cell-Dyn Sapphire, Abbott Diagnostics). To evaluate hemolysis, Hb in plasma was measured on a plasma/low Hb photometer (HemoCue, HemoCue AB) and percent hemolysis wad calculated as $((\text{plasma-Hb}/10) \times (100 - \text{Hct}))/\text{Hb}$.

Blood gas variables (pH, pO_2, pCO_2, and base excess [BE]) were analyzed on a blood gas analyzer (ABL825 FLEX, Radiometer Medical ApS). Sodium and potassium, glucose, and lactate levels were measured on a chemistry analyzer (Cobas 8000, ISE/c702, Roche Diagnostics GmbH).

The effects of storage on coagulation were studied by measuring activated partial thromboplastin time (aPTT), prothrombin time/international normalized ratio (INR), Factor (F)VIII and fibrinogen using a hemostasis analyzer (STA-R Evolution/STA-R Max; STA-Liquid Fib/STA-Fibrinogen 5, STA-Deficient VIII, STA-SPA+, STA-PTT Automate 5, STA-CaCl2 and STA-Unicalibrator, Stago S.A.S.).

The hemostatic function was evaluated by kaolin-initiated thromboelastography on a thromboelastograph (TEG 5000, Haemonetics Corporation) and quantified as time to start of clot formation, clot formation speed (angle), and maximum achieved clot strength (MA).

To quantify PLT aggregation, we performed multiplate impedance aggregometry (Roche Diagnostics GmbH) with 6.5 μmol/L adenosine diphosphate (ADP), and light transmission aggregometry (LTA; Chrono-log Model 700, Chrono-log Corporation) with 10 μmol/L ADP and 30 μmol/L thrombin receptor-activating peptide 6 (TRAP-6, Roche Diagnostics GmbH).

Samples for impedance aggregometry were analyzed using the manufacturer's procedure for citrated samples, including partial recalcification with 3 mmol/L $CaCl_2$. PLT-rich plasma (PRP) for LTA was prepared by $200 \times g$ centrifugation for 10 minutes. The remaining material was further centrifuged at $1500 \times g$ for 15 minutes to yield PLT-poor plasma. PLT count in PRP was verified to be in the 150×10^9 to 600×10^9/L range.[20] PRP and PLT-poor plasma was visually inspected for hemolysis and lipemia and incubated at 37°C for 3 minutes before performing LTA at 37°C with 1000 RPM stirring. Samples were run in two parallels, and the mean was reported.

Platelet activation and adhesion were also investigated in 8 control units and 6 HEMS units by use of flow cytometry. Samples were stimulated with 2,8 μL ADPtest and 1,7 μL TRAPtest. A premade mix of monoclonal mouse anti-human antibodies were thereafter added without further incubation (BD Bioscience) with PerCP CD61 (Clone EUU-PL 7 F12, Cat. No. 347408), APC CD42b (Cat. No. 551061), and PE CD62P (Cat. No. 561921). Thirty minutes of incubation in the dark at room temperature was followed by a RBC lysing step where we added 465 μL of lysis buffer (Dako EasyLyse, Ref. No. S2364, Agilent). After 2 mL of flow cytometry sheath fluid (FACSFlow, Cat. No. 342003, BD Biosciences) was added, the samples were run on a flow cytometer using its software (BD FACSCanto II and FACSDiva, Version 8.0.1, respectively, BD Biosciences). We gated the PLTs using forward scatter height versus area to avoid doublets and side scatter versus forward scatter to narrow the gating. The same gating was used

on all samples, regardless of age. Results reported as age of percent parent of CD61-positive cells for the activation markers.

Statistical analysis

The effect of forward storage in an airtight container at the HEMS base on each of the outcome variables was investigated using a linear mixed-effect model with storage time, study group, and their interaction as predictors. In this model, we used simple contrasts to investigate whether the outcome variables changed from Day 1 to 8, Day 1 to 14, and Day 1 to 21. Additionally, we used the interaction between storage time and study group to describe whether this level of change was different between the blood stored at the blood bank and at the HEMS base. The p value reported in the text and figures are for this interaction. Potential differences in age and sex distribution between the two groups were examined using independent-sample t tests. A p value of less than 0.05 was considered significant. Results were presented as mean (95% confidence interval [CI]). All analyses were performed with computer software (R version 3.6.0 with the NLME package version 3.1-140, The R Foundation for Statistical Computing).

We found no previous studies that could be used for sample size calculation. With the general assumption of normality for outcome measures enabling the use of a two-sided t-test, setting the mean to 1 and a standard deviation to 0.5 with a significance level of 0.05 and a power of 0.8, we found that we needed a minimum of 17 individual units in each group. Based on this we chose to include 20 WB units in each study group.

RESULTS

Quality requirements

A total of 40 CWB units were monitored and tested, 20 in the HEMS group and 20 in the control group. During storage at the HEMS base, there were no recorded breaches of temperature limits (1-10°C). Table 1 show the number of HEMS missions in which CWB were carried and the total duration of storage outside of the refrigerator. The blood was carried on a mean (95% CI) number of 4.1 (2.86-5.34) missions. The mean (95% CI) duration of the missions was 339 (209-469) minutes.

All units in the study complied with the requirements set forth in the "Guide to the Preparation, Use and Quality Assurance of Blood Components."[19] The hemolysis at the end of storage was below the EU requirement of 0.8% of the RBC mass in all units throughout storage in both groups. The Hb level was above the EU requirements of 43 g/unit in all observed units until the end of storage (Table S1, available as supporting information in the online version of this paper).

TABLE 1. Number and duration of HEMS missions where WB units were carried*

WB unit	Number of missions	Mission duration (min)
1 & 2	3	120
3 & 4	6	600
5 & 6	3	180
7 & 8	6	360
9 & 10	6	420
11 & 12	2	180
13 & 14	4	300
15 & 16	3	360
17 & 18	6	660
19 & 20	2	210

* There were no recorded temperature breaches.

Changes during 21-day storage

Hematology

There was no significant difference in change during storage regarding PLT count, mean PLT volume, or number of RBCs between the two groups (Fig. 1A, Table S1). We found a statistically significant difference in the change of Hb levels from Day 1 to Day 21 between the two groups ($p < 0.05$; Fig. 1B).

Clinical chemistry

We found no significant difference in change in potassium between the two groups during 21 days of storage (Fig. 1C).

Metabolism

When investigating how the metabolic markers changed in the two groups, we found that the glucose concentration declined more in the HEMS group on Days 8, 14, and 21 ($p < 0.05$) compared to the control group (Fig. 1D). The same was evident in regard to pH and BE (Fig. 1E and Table S1). Conversely, we found that the lactate increased significantly in the HEMS group compared to the control group (Fig. 1F).

Hemostatic properties

There was no significant difference in change in fibrinogen, international normalized ratio and FVIII levels (Figs. 1G and 1H and Table S1). However, we found a reduction in aPTT on Day 21 in the test group (Fig. 1I). When investigating the change in hemostatic capacity by thromboelastography, we found no difference in change during storage regarding time to start of clot formation and K between the two groups (Fig. 1J and Table S1). However, we found that the TEG angle declined less in the HEMS group compared to the control group on Days 8, 14, and 21 ($p < 0.05$; Fig. 1K). This was also observed in regard to TEG MA, where the TEG MA declined less in the HEMS group (Fig. 1L). As discussed later, we also observed significant differences between the two groups at baseline.

When investigating the PLT aggregation capacity by the use of the multiplate analyzer with ADP test, we found no

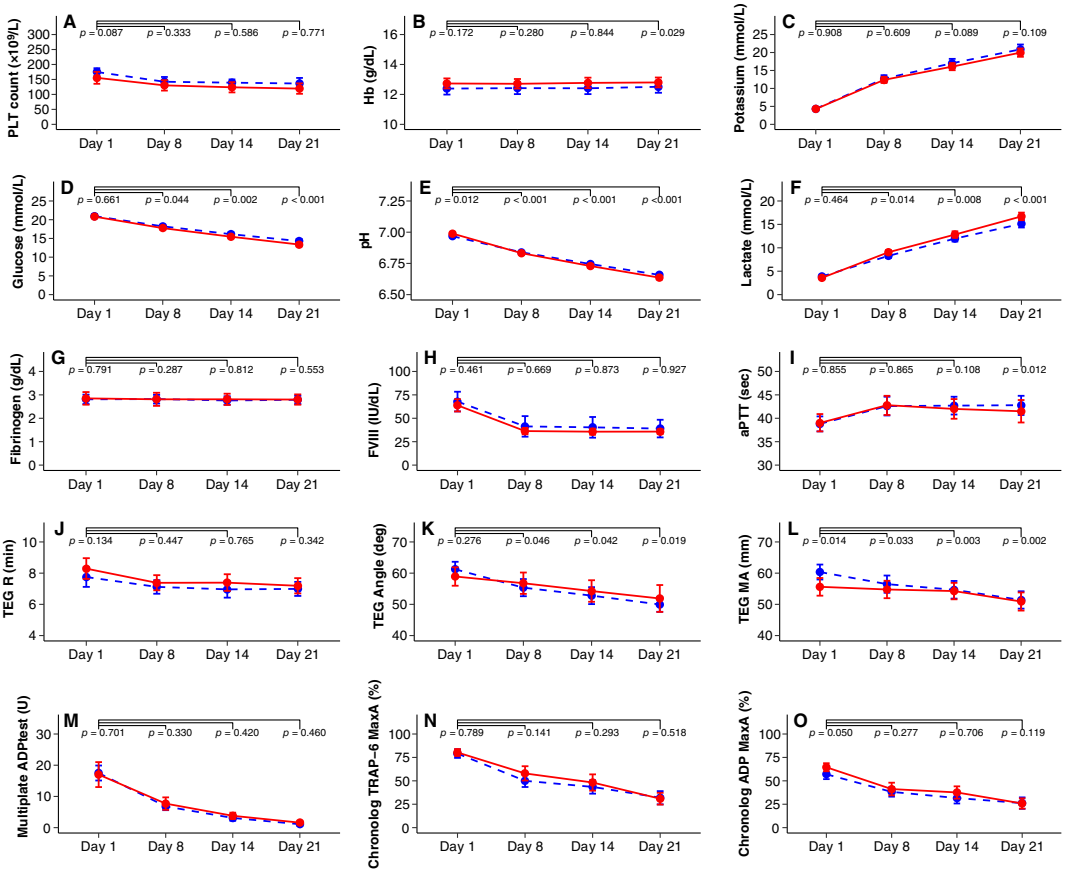

Fig. 1. Mean and 95% CIs of the variables during 21 days of storage. (------) Control group; (——) HEMS group. A linear mixed-effects model with storage time, study group, and their interaction as predictors was fitted. The p value shown represents the interaction between storage time and study group and signifies whether there was a significant difference between the two groups in how the variable changed from Day 1 to 8, Day 1 to 14, and Day 1 to 21. [Color figure can be viewed at wileyonlinelibrary.com]

significant difference during storage between the two groups (Fig. 1M). There were also no differences between the two groups when utilizing LTA to assess maximum aggregation with TRAP and ADP as stimulants (Figs. 1N and 1O). The spontaneous aggregation was comparable in the two groups (Table S1). Finally, in regard to PLT function, we found no significant difference between the two groups when investigating ADP- and TRAP-stimulated expression of CD62P and CD42b by flow cytometry (Table S1).

Additional findings

We found a statistically significant difference in pH, BE, and TEG MA on Day 1, indicating that there was a difference between the two groups at baseline in these variables. There were no significant differences between the groups in the distribution of donor ages (HEMS 36.2 [30.3-42.1] versus control 42.6 [36.1-49.1]; p = 0.134) and sex (HEMS 15 male, five female vs. control nine male, 11 female; p = 0.053).

DISCUSSION

This study evaluated changes in hematology, clinical chemistry, metabolism, and hemostatic variables of CWB stored in an airtight thermal box forward at a HEMS base, for up to 21 days, compared to changes of CWB stored according to routine practice in the blood bank. All CWB units complied

with the requirements set forth in the "Guide to the Preparation, Use and Quality Assurance of Blood Components" throughout storage for 21 days, regardless of storage conditions. The hemolysis grade was below 0.8% of the total RBC mass, and that the Hb content was above 43 g/unit.[19]

The storage of CWB at the HEMS base revealed no safety concerns concerning temperature limits (1-10°C). This is important as increased temperature may compromise the product quality.[21–23] Thus, the crew must be vigilant in monitoring the operability of the refrigerator and to ensure that there has not been breach of temperature limits before administering the blood in the field. Temperature monitoring is an essential part of quality control in transfusion medicine. One of the main disadvantages of the present storage container is that the crew must open the box to read the logger. Future designs should consider providing an external temperature reading on the thermal box to improve safety.[24]

The number of missions varied from two to six, and the total duration of missions varied from 120 to 660 minutes for the blood units in the HEMS group. In addition to changes in temperature, the blood properties could potentially be influenced by changes in pressure and vibration during missions. Due to the low number in each group, we were not able to adjust for differences in the amount and duration of missions in the results. However, if these factors were substantial, we would expect the variance of the results in the HEMS group to be generally larger than that in the control group (Table S1). Generally, for all our outcome measures small CIs were observed in both groups.

We found a significant difference in how the Hb levels had changed in the two groups at 21 days of storage. However, the difference between the two groups is without clinical significance as the difference in change of Hb concentration between the two groups was only 0.05 g/dL.

Prehospital CWB is stored in an airtight thermal box and placed inside a conventional refrigerator at the HEMS base. The changes in metabolic variables during storage and comparison between the two groups suggest that there are minor alterations in gas exchange conditions for CWB stored in airtight thermal insulated storage containers. We observed slightly higher lactate levels and lower BE and pH levels in CWB stored forward. The clinical impact of these values is uncertain and probably without importance. There was a significant difference in how aPTT had changed at 21 days, with less increase in the HEMS group on Day 21. The difference was minimal and for the benefit of the HEMS group, however, probably without clinical significance.

Viscoelastic hemostatic capacity as measured by TEG was present in both groups for the entire 21-day storage period. As mentioned, we found that the TEG angle had declined less in the HEMS group. The TEG angle measures the speed at which fibrin builds up and cross-links. Hence, the angle assesses the rate of clot formation. This process is propagated by thrombin formation and is dependent on PLTs and fibrinogen. We did not find that there was a significant difference in these measurements on Day 1, nor any difference in how these variables changed. Based on this, it seems unlikely that the difference in the TEG angle can be explained by PLT and fibrinogen effects. Further, there was also a significant difference in the TEG MA evolution during storage. Again, it declined less in the HEMS group. The TEG MA represents in simple terms the ultimate strength of the fibrin clot, dependent on PLT function and fibrin levels. We did not find significant differences when evaluating PLT count and function using LTA and multiplate or flow cytometry.

When it comes to the hemostatic properties of CWB in general, these results show that viscoelastic hemostatic properties are to a great extent maintained for up to 21 days. The final MA in both groups was approximately 50, whereas the plasma fibrin contribution to clot strength alone typically yields an MA of 10.[25] This indicates that the PLTs in CWB retain considerable ability to catalyze clot formation and contraction throughout storage duration. The PLT function as measured by PLT aggregation and agonist-induced glycoprotein expression was preserved for at least up to 8 days of storage, after this we observed a decline in response. This is consistent with previous studies.[26–28]

We found significant differences in pH, BE, and TEG MA, between the two groups on Day 1. We performed secondary analysis to see if the differences were related to the distributions of sex and age between the groups but did not find a statistical relationship. However, examining the data, although not significant, the mean PLT count was 175 in the control group versus 155 in the HEMS group. The TEG MA is affected by PLT count, and this may explain this finding. Regarding pH and BE, although there were significant differences at baseline, the actual values are without clinical significance (mean pH 6.97 in control group vs. 6.99 in HEMS group). Further, these findings should not interfere with secondary objective results as the statistical design takes into account differences at baseline.

We conclude that storage of CWB in thermal containers in a prehospital emergency service is feasible. The logistics and maintenance of the thermal conditions are easy and safe. The product quality is within EU regulations for up to 21 days of storage. The hemostatic properties of CWB stored prehospital are similar to those of CWB stored in the blood bank. The PLT function in CWB deteriorates after 8 days of storage but is still clinically useful for up to 21 days. These findings support the practice of extending storage in resource-poor environments and thus reducing waste.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

1. Yazer MH, Spinella PC. The use of low-titer group O whole blood for the resuscitation of civilian trauma patients in 2018. Transfusion 2018;58:2744-6.
2. Curry NS, Davenport R. Transfusion strategies for major haemorrhage in trauma. Br J Haematol 2019;184:508-23.
3. Cap AP, Pidcoke HF, Spinella P, et al. Damage control resuscitation. Mil Med 2018;183:36-43.
4. Holcomb JB. Damage control resuscitation. J Trauma 2007;62: S36-7.
5. Cantle PM, Cotton BA. Balanced resuscitation in trauma management. Surg Clin North Am 2017;97:999-1014.
6. Eckel AM, Hess JR. Transfusion practice in trauma resuscitation. South Med J 2017;110:554-8.
7. Spinella PC, Cap AP. Prehospital hemostatic resuscitation to achieve zero preventable deaths after traumatic injury. Curr Opin Hematol 2017;24:529-35.
8. Krook C, O'Dochartaigh D, Martin D, et al. Blood on board: the development of a prehospital blood transfusion program in a Canadian helicopter emergency medical service. CJEM 2019; 21:365-73.
9. Yazer MH, Spinella PC, Allard S, et al. Vox Sanguinis International Forum on the use of prehospital blood products and pharmaceuticals in the treatment of patients with traumatic haemorrhage. Vox Sang 2018;113:701-6.
10. Bjerkvig CK, Strandenes G, Eliassen HS, et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion 2016;56(Suppl 2):S182-9.
11. Spinella PC, Reddy HL, Jaffe JS, et al. Fresh whole blood use for hemorrhagic shock: preserving benefit while avoiding complications. Anesth Analg 2012;115:751-8.
12. Cordova CB, Capp AP, Spinella PC. Fresh whole blood transfusion for a combat casualty in austere combat environment. J Spec Oper Med 2014;14:9-12.
13. Strandenes G, Berseus O, Cap AP, et al. Low titer group O whole blood in emergency situations. Shock 2014;41(Suppl 1): 70-5.
14. Strandenes G, Hervig TA, Bjerkvig CK, et al. The lost art of whole blood transfusion in austere environments. Curr Sports Med Rep 2015;14:129-34.
15. Fisher AD, Washbum G, Powell D, et al. Damage control resuscitation in prolonged field caredamage control resuscitation in prolonged field care. J Spec Oper Med 2018;18:109-19.
16. Belin TR, Yazer MH, Meledeo MA, et al. An evaluation of methods for producing low-titer group O whole blood to support military trauma resuscitation. J Trauma Acute Care Surg 2017;82:S79-86.
17. Strandenes G, De Pasquale M, Cap AP, et al. Emergency whole blood use in the field: a simplified protocol for collection and transfusion. Shock 2014;41(Suppl 1):76-83.
18. Karl A, Pham T, Yanosky JD, et al. Variability of uncrossmatched blood use by helicopter EMS programs in the United States. Prehosp Emerg Care 2016;20:688-94.
19. Guide to the preparation, use and quality assurance of blood components [Internet]. Strasbourg: EQDM Council of Europe; 2017 [cited 18 Aug 2019]. Available from: https://www.edqm.eu/en/blood-transfusion-guide.
20. Cattaneo M, Cerletti C, Harrison P, et al. Recommendations for the standardization of light transmission aggregometry: a consensus of the working party from the Platelet Physiology Subcommittee of SSC/ISTH. J Thromb Haemost 2013;11: 1183-9.
21. Brunskill S, Thomas S, Whitmore E, et al. What is the maximum time that a unit of red blood cells can be safely left out of controlled temperature storage? Transfus Med Rev 2012;26: 209-23 e3.
22. Nilsson L, Hedner U, Nilsson IM, et al. Shelf-life of bank blood and stored plasma with special reference to coagulation factors. Transfusion 1983;23:377-81.
23. Blaine KP, Cortes-Puch I, Sun J, et al. Impact of different standard red blood cell storage temperatures on human and canine RBC hemolysis and chromium survival. Transfusion 2019;59: 347-58.
24. Aalaei S, Amini S, Keramati MR, et al. Blood bag temperature monitoring system. Stud Health Technol Inform 2014;205: 730-4.
25. Bochsen L, Wiinberg B, Kjelgaard-Hansen M, et al. Evaluation of the TEG platelet mapping assay in blood donors. Thromb J 2007;5:3.
26. Strandenes G, Austlid I, Apelseth TO, et al. Coagulation function of stored whole blood is preserved for 14 days in austere conditions: a ROTEM feasibility study during a Norwegian antipiracy mission and comparison to equal ratio reconstituted blood. J Trauma Acute Care Surg 2015;78:S31-8.
27. Pidcoke HF, McFaul SJ, Ramasubramanian AK, et al. Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. Transfusion 2013;53(Suppl 1):137S-49S.
28. Meledeo MA, Peltier GC, McIntosh CS, et al. Optimizing whole blood storage: hemostatic function of 35-day stored product in CPD, CP2D, and CPDA-1 anticoagulants. Transfusion 2019;59: 1549-59.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Mean and 95% confidence intervals for all measured variables. A linear mixed effect model with storage time, study group and their interaction as predictors was fitted. For time, simple contrasts were used. p_{Day} signifies whether there was a statistically significant change from Day 1 to the specified storage day. $p_{Interaction}$ signifies whether this change was statistically different between the two study groups. The $p_{Interaction}$ given for Day 1 indicates whether the baseline measurement was significantly different in the two groups..

III

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Prehospital Whole Blood Transfusion Programs in Norway

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Abstract

Background: Prehospital management of severe hemorrhage has evolved significantly in Norwegian medical emergency services in the last 10 years. Treatment algorithms for severe bleeding were previously focused on restoration of the blood volume by administration of crystalloids and colloids, but now the national trauma system guidelines recommend early balanced transfusion therapy according to remote damage control resuscitation principles. ***Materials and Methods:*** This survey describes the implementation, utilization, and experience of the use of low titer group O whole blood (LTOWB) and blood components in air ambulance services in Norway. Medical directors from all air ambulance bases in Norway as well as the blood banks that support LTOWB were invited to participate. ***Results:*** Medical directors from all 13 helicopter emergency medical services (HEMS) bases, the 7 search and rescue (SAR) helicopter bases, and the 4 blood banks that support HEMS with LTOWB responded to the survey. All HEMS and SAR helicopter services carry LTOWB or blood components. Four of 20 (20%) HEMS bases have implemented LTOWB. A majority of services (18/20, 90%) have a preference for LTOWB, primarily because LTOWB enables early balanced transfusion and has logistical benefits in time-critical emergencies and during prolonged evacuations. ***Conclusion:*** HEMS services and blood banks report favorable experiences in the implementation and utilization of LTOWB. Prehospital balanced blood transfusion using whole blood is feasible in Norway.

Introduction

Prehospital management of severe hemorrhage has evolved significantly in Norwegian medical emergency services in the last 10 years [1–3]. Treatment algorithms for severe bleeding were previously focused on restoration of the blood volume by administration of crystalloids and colloids, but today, the national trauma system guidelines recommend balanced transfusion therapy as early as possible [4, 5]. In Norway, military-civilian cooperation has been instrumental in facilitating this shift in policy. The initial step was the implementation of freeze-dried plasma (FDP), followed by red blood cell (RBC) concentrates and low titer group O whole blood (LTOWB) at some of the air ambulance bases. This paradigm shift is based on recent scientific progress in remote damage control resuscitation, which states that life-threatening hemorrhage requires immediate intervention and resuscitation with blood and blood products to reduce the impact of hemorrhagic shock, including subsequent coagulopathy and organ failure, to increase survival and reduce morbidity [6–10]. Evidence from military and civilian

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practice suggests that early administration of blood may improve survival to the hospital, decrease ongoing transfusion requirements, and decrease mortality [11]. Coagulopathy of trauma is a process that occurs in patients suffering from hemorrhagic shock after major trauma. It has become evident that the duration and severity of shock influence the degree of coagulopathy, the activation of inflammation and overall clinical status when the patient is admitted to the emergency room. Studies have demonstrated that platelet dysfunction and fibrinogen deficiency are of paramount importance in early trauma-induced coagulopathy [12–15]. An early balanced transfusion strategy addresses both critical oxygen delivery due to the loss of volume, the ability to form clots at bleeding sites and the prevention of endotheliopathy [16–19].

Current evidence supports the implementation of LTOWB in prehospital services. A major challenge is the limited availability of platelet concentrates, as most institutions utilize room temperature-stored platelets under constant agitation with a maximum holding time of 5–7 days. Therefore, a true balanced component-based transfusion strategy is difficult to achieve in the prehospital environment. In addition, whole blood-based transfusion therapy causes reduced hemodilution due to the relatively reduced amount of additive solution in LTOWB compared to a balanced component transfusion alternative [20]. Furthermore, the simplicity of the logistics involving LTOWB is advantageous because it is easier to prepare and transfuse single units of LTOWB compared to separate bags for plasma, red cells, and platelets during prehospital time-dependent critical emergencies.

The aims of this study were to describe Norwegian prehospital air ambulance blood transfusion programs, to describe the rationale for and the practical aspects of implementation of a prehospital LTOWB program, and to present the experience with LTOWB in Norway from the air ambulance and blood banking perspective.

Materials and Methods

Study Design and Ethics

This was a survey of the implementation, utilization, and experience with the use of blood products in the HEMS and SAR helicopter services in Norway with a focus on our LTOWB program. This survey was conducted and funded by the Department of Immunology and Transfusion Medicine and the Department of Anesthesia and Intensive Care, Haukeland University Hospital (Bergen, Norway). No information on individual patients were collected. The local data protection officer reviewed the survey.

The Norwegian System for Prehospital Critical Care

The Norwegian healthcare system is organized into four different government-funded regional health authorities that administer hospital systems in the regions. Prehospital critical care is the joint responsibility of municipal health services, regional ground ambulance services, the civilian National Air Ambulance Services of Norway, and military and civilian search and rescue (SAR) helicopters. In Norway, the combination of fjords, mountains, and scattered populations often results in long transport times to hospitals. Due to bad weather conditions, communities may also be isolated for days at a time.

The National Air Ambulance Services of Norway are responsible for helicopter emergency medical services (HEMS) and fixed wing air ambulances in Norway. This nationwide service operates 14 helicopters located at 13 bases and 9 fixed wing aircraft located at 7 bases [21] and responds to all types of medical emergencies 24 h a day every day. More than 20,000 patients are supported yearly by helicopter or a rapid response car. Although the primary role of HEMS is to respond to medical and trauma cases, it also handles pediatric and neonatal retrievals, interhospital transfers, and SAR missions. The service is government funded, but the regional health authorities administer the bases. Hence, there are some differences in the medical capabilities and standard operating protocols among the bases. The HEMS are staffed with a prehospital anesthesiologist at the consultant level, a HEMS rescue paramedic, and a pilot. The HEMS conduct missions in almost all weather conditions, including instrument flying conditions or visual flying conditions with night vision capabilities. The national dispatch strategy aims to reach 90% of the population within 45 min after dispatch.

The Norwegian SAR helicopters are largely operated by the Royal Norwegian Air Force. SAR is funded by the Ministry of Justice and Public Security and operates 6 bases along the coastline of Norway. A civilian contractor operates an additional base at Svalbard. The Norwegian SAR helicopter services area of responsibility is extensive and primarily focuses on the vast sea territories bordering Norway and the Arctic regions, but they also respond to ambulance missions when needed. Two pilots, two system operators, a rescue swimmer, and a prehospital anesthesiologist at the consultant level normally operate on SAR helicopters. The civilian SAR helicopter at Svalbard has the same medical capabilities as military SAR helicopters.

The Norwegian Blood Bank Structure

Norwegian blood banks are hospital based, and their activities include blood collection, component production, and storage in addition to in-hospital immunohematology and transfusion services. The blood banks adhere to EU regulations and standards [22]. All hospitals in Norway have their own blood banks, but many of the smaller blood banks do not provide platelet concentrates due to low demand and the risk of waste. Whole blood for transfusion is made available for in-hospital use by some blood banks, whereas the use of whole blood is under discussion in others. Because the blood bank system is decentralized, accessibility of LTOWB to the different air ambulance bases is dependent on local blood bank policies.

Data Collection

The medical directors of the 13 HEMS bases and 7 SAR helicopter bases were contacted by telephone and invited to participate in the survey. The aims of the survey were explained, and the telephone call was followed by an electronic questionnaire sent by email. In the case of missing responses, the medical directors were contacted again by phone. A similar approach was applied to the blood banks supporting HEMS bases with LTOWB.

Three sets of questions were used: one for the ambulance bases that had implemented LTOWB, one for bases that had not implemented LTOWB, and a separate survey for the blood banks that support prehospital LTOWB.

Table 1. Blood and hemostatic adjunct inventory in SAR and HEMS in Norway

Inventory	Total (*n* = 20)	Components (*n* = 16)	WB (*n* = 4)
RBC	13 (65%)	13 (81%)	0 (0%)
FDP	20 (100%)	16 (100%)	4 (100%)
LTOWB	4 (20%)	0 (0%)	4 (100%)
TXA	20 (100%)	16 (100%)	4 (100%)
Calcium chloride/calcium gluconate	16 (80%)	13 (81%)	3 (75%)
Fibrinogen concentrate	6 (30%)	5 (31%)	1 (25%)
Prothrombin complex concentrate	2 (10%)	1 (6%)	1 (25%)

RBC, red blood cells; FDP, freeze-dried plasma; LTOWB, low titer group O whole blood; TXA, tranexamic acid.

Statistical Analysis

Descriptive statistics were performed using Prism 9 v. 9.1.2 for Mac – GraphPad Software LLC. Results are shown as medians (IQR, min.–max.). No statistical comparisons were performed between the services providing LTOWB and those not providing LTOWB due to the low numbers.

Results

All medical directors from the 13 HEMS and 7 SAR bases and the 4 blood banks that supply LTOWB responded to the surveys, yielding a response rate of 100%. Only one response per service was received.

Prehospital Blood Inventory in Norway

All 20 Norwegian HEMS and SAR services carry dried plasma. In addition, 13/20 (65%) services carry RBC concentrates, and 4/20 (20%) carry LTOWB (Table 1). The variation in the blood inventory is shown in Figure 1. All services carry tranexamic acid in addition to various hemostatic adjuncts, such as fibrinogen concentrate and prothrombin complex concentrate (Table 1). Calcium supplementation is included in the transfusion protocols for a majority of the services. No services carry frozen plasma, platelet concentrates, albumin, or desmopressin. With one exception, all services store the blood and blood products at the base, ready for emergency response. One HEMS service collects RBCs at the hospital but FDP is available at the base. HEMS implemented battery-powered blood warmers in 2021. SAR services have procured blood warmers, but some still await implementation.

The number of transfusion episodes in 2020 in Norway is shown in Figure 2. In total, there were 216 prehospital transfusion events. The median number of transfusions per base was 8.5 (4.3–18, 0–28). The number of transfusions varied based on location and type of service. SAR services generally have the lowest number of transfusions.

Fourteen of the 16 (88%) services that did not carry LTOWB stated that they wished to implement LTOWB in the future. In total, 18 of the 20 (90%) Norwegian HEMS and SAR services preferred LTOWB in the prehospital service, and only 2 of the 20 (10%) reported that they had not decided on a future strategy concerning LTOWB. None answered that they did not wish LTOWB. One of the services that only carries FDP stated a goal to implement RBCs in the future.

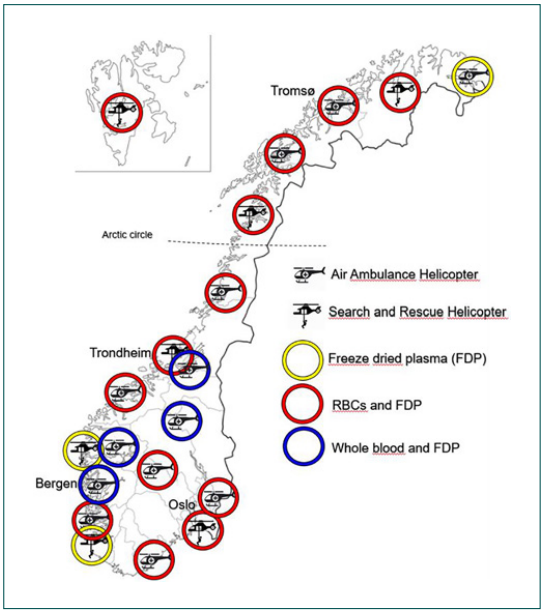

Fig. 1. The location and inventory of the HEMS and SAR helicopter bases in Norway.

The medical directors who had requested LTOWB from their local blood banks reported the following challenges in the potential implementation of LTOWB: (1) LTOWB is not currently available at their supporting blood bank; (2) there is a need for evidence on efficacy and safety in the implementation of LTOWB in HEMS

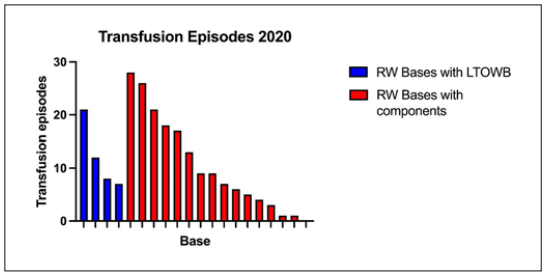

Fig. 2. The number of transfusion events at the individual HEMS and SAR helicopter base in 2020.

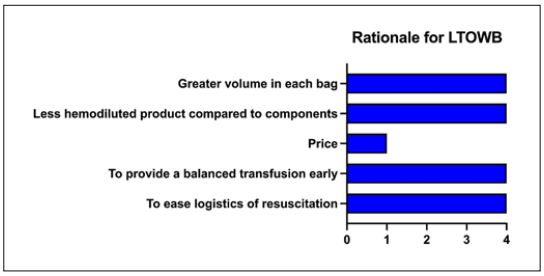

Fig. 3. The rationale for implementation of LTOWB at the four HEMS bases.

and SAR services to present when discussing with the blood bank; (3) negative cost-benefit analysis due to few potential transfusions annually, including concerns with respect to the potential for waste; and (4) concerns expressed by the local blood bank with respect to a lack of LTOWB donors.

Prehospital LTOWB in Norway

Four of the 20 (20%) services have implemented LTOWB, all of which are HEMS bases. The first service initiated their LTOWB program in 2015, the second in 2017, and the last two in 2019 and 2021. Prior to the implementation of LTOWB, the services had RBCs and FDP available. Figure 3 shows the rationales given for implementing LTOWB. The four (20%) bases all store two units of LTOWB in temperature-monitored thermal containers (Credo Duracube HD with Golden Hour inner container, Pelican BioThermal) within a refrigerator at the base. The storage time is 7 days at two of the bases and 14 days at the other two. There were no reports on breaches in cold chain storage.

Only one base reported that LTOWB was carried on every mission. Others reported that the individual crew decided whether blood was to be included depending on the nature of the emergency dispatch. The reasons for not including blood on every mission were the limited space and weight restraints for the helicopter and the risk of breaking the cold chain if the blood was forgotten in the cabin of the helicopter. One of the directors commented that a powered, fixed cooler suitable for the helicopter would be beneficial.

All bases reported that the doctor on call decides whether to initiate a whole blood transfusion. Three of the four bases stated that they have a supporting transfusion protocol but that the transfusion triggers are broad with the decision relying on the clinical judgment and experience of the crew. No respondents reported any suspected transfusion reactions since the initiation of the LTOWB programs.

When the respondents were asked to subjectively assess the logistical burden of the LTOWB program from a numeric scale (1–10) where 1 is minimal and 10 is severe, two bases reported 2 and two bases reported 1.

Information from Blood Banks Supporting LTOWB for Prehospital Transfusion

All four blood banks supporting HEMS with LTOWB provide Rhesus D-negative whole blood. The definitions of low titers implied are as follows: IgM anti-A and anti-B <250 and IgG anti-A and anti-B <500 for three of the blood banks, whereas the fourth blood bank defines low titers as IgM and IgG anti-A and anti-B <256. Different column/gel agglutination techniques are applied for the measurement of titer. Two blood banks use male donors only, while two include both male and female donors. No additional testing is required for female donors. Three blood banks stated that they had sufficient LTOWB donors, while one stated that they had challenges from time to time with supply.

All blood banks provide LTOWB with citrate phosphate dextrose, which is leukoreduced with a platelet-sparing filter (Terumo Imuflex® WB-SP). If whole blood is used, two of the blood banks resupply the HEMS base with RBCs between the preplanned whole blood exchange dates, while one blood bank answered that they are usually able to substitute one unit of LTOWB. The fourth blood bank uses LTOWB in the hospital massive transfusion packages with a minimum inventory of 8 LTOWB units at any time and is therefore able to resupply HEMS with LTOWB when needed.

LTOWB that is not transfused during the predefined storage time at the HEMS base is returned to the blood bank. Two blood banks utilize LTOWB that is not used at HEMS for in-hospital patients, whereas for the other two blood banks, the units are outdated and discarded. The waste rates were 79.6%, 73.2%, 77.0%, and 26.4% for the four different blood banks, with the lowest waste rate observed at the blood bank that regularly utilizes whole blood for in-hospital massive transfusion packages.

Two blood banks followed every prehospital transfusion with registration in a local quality registry and/or posttransfusion hemolysis panel. Two blood banks did not have follow-up protocols after transfusion. All respondents stated that their overall experience in providing LTOWB for HEMS was favorable.

Discussion

This survey provides an overview of the Norwegian HEMS and SAR helicopter service capabilities, experiences, and future visions for prehospital blood transfusion. There has been a significant shift in strategy since 2012, when no service had blood readily available at the base. Some of the services had an option to pick up blood at the blood bank, but crystalloid and colloid therapy was the backbone of fluid resuscitation. Recent evidence has highlighted the importance of early aggressive hemostatic resuscitation of hemorrhagic shock both in civilian and military settings. Shackelford et al. [23] found that prehospital blood product transfusion in the military setting was associated with increased 24-h and 30-day survival. In a civilian setting, studies of early prehospital transfusion have shown a significant reduction in mortality in patients with bleeding without a significant increase in harm [24, 25]. With a population of only 5.4 million across an area of 385,000 km^2, Norway has a demanding topography consisting of mountains and fjords, which may make ground ambulance transport of critical trauma patients challenging. Furthermore, the long distances between Norwegian Level 1 trauma centers (approximately 600 km) support the use of air transport and demand that HEMS use a remote damage control resuscitation approach for critical patients [3].

In Norway, experienced prehospital anesthesiologists at consultant level staff the HEMS and SAR helicopter services. Although most services utilize transfusion protocols with evaluation of common transfusion triggers (mechanism of injury compatible with hemorrhage, blood pressure <100 mm Hg, pulse rate >90 bpm, lactate >4 mmol/L, and impaired mentation), the services emphasize the overall clinical judgment of the doctor on call. The low overall number of transfusion episodes reported in 2020 likely reflects the relatively small trauma population in Norway.

The differences in inventory and strategy at the SAR and HEMS services in Norway are explained by differences in local policies and the availability of LTOWB at the blood banks supporting the different services. However, the national trauma guidelines that state that services should be able to provide an early balanced transfusion strategy have had an impact, as all HEMS and SAR helicopter services now carry LTOWB or blood components.

Civilian-military cooperation has been of instrumental importance for the implementation of LTOWB in Norway [26–28]. Initial protocols for cold-stored LTOWB were initiated to support the Norwegian Armed Forces with trauma resuscitation in international operations in 2013. This development seems to be consistent with the increasing implementation of cold-stored LTOWB in civilian systems in other countries [29, 30].

Almost all HEMS and SAR services prefer LTOWB in the prehospital service. The predominant reasons seem to be linked to the logistical benefits of LTOWB transfusions for provision of a balanced transfusion in time-dependent critical emergencies where there often is lack of personnel, a goal to reduce on-scene time to a minimum, and constrained working spaces during the flight. This is consistent with experience from the HEMS in London, UK. To mitigate these challenges, they are performing a 2-year feasibility study on the utilization of a combined red cell and plasma component for forward resuscitation to reduce the workload and time spent on the scene [31]. The responders also highlight the ability to provide a balanced transfusion to bleeding patients, which is in accordance with Norwegian national and international guidelines [4, 32]. In-hospital studies suggest that RBCs, plasma, and platelets should be given together in a 1:1:1 ratio [33, 34]. Furthermore, LTOWB may be of benefit since platelets may be more effective if given early [35]. Finally, the respondents emphasize the impact of larger volumes in each bag, further highlighting the importance of reducing the workload during resuscitation.

In a previous study, we evaluated the safety and hemostatic properties of LTOWB stored at the air ambulance base [36]. The study concluded that forward storage of LTOWB is feasible, easy, and safe and that the product quality is within EU regulation standards during storage. Platelet function seems to deteriorate after 8 days of storage but is still clinically useful for up to 21 days [36]. Three of the blood banks that supply HEMS with LTOWB report relatively high waste levels (>70%). In Norway, with a relatively small population and a small number of trauma cases, it seems that hospitals need to accept high waste levels of LTOWB to implement its use in the HEMS system. On the other hand, as demonstrated by one of the respondents, if the blood bank facilitates in-hospital transfusions of LTOWB, waste might be considerably mitigated. The blood bank that utilizes LTOWB for massive transfusion in the hospital rotates unused LTOWB units at the HEMS to the hospital and reports a waste level of approximately 26%.

Increasing numbers of hospitals, especially in the USA, have included LTOWB in their in-house emergency massive transfusion protocols. Data suggest that transfusion of uncrossmatched LTOWB for catastrophic hemorrhage in the hospital is safe and that there is no significant dif-

ference in survival rates between nongroup O patients receiving incompatible plasma and group O patients receiving compatible plasma [37–40]. The available literature supports the feasibility and safety of LTOWB used in the treatment of civilian patients, but the evidence regarding clinical outcomes, particularly with direct comparison to balanced-ratio transfusions with components, is limited [29, 41]. Hence, with respect to hard endpoints, there is not enough evidence to support or refute the clinical superiority of LTOWB compared to component therapy. However, there are three ongoing randomized controlled trials for early trauma resuscitation with whole blood for severely bleeding patients [42–44].

Respondents to the survey indicated several challenges in the potential implementation of LTOWB. Most commonly, there was a lack of availability of LTOWB at the local blood bank and a lack of evidence for efficacy and safety when arguing their case to blood providers. The results from ongoing studies and clinical experience from current users are essential for the future use of LTOWB in prehospital emergency care services.

The strengths of this study include the high response rate from survey participants (100%) and the level of detail in the information given. Limitations include a potential uncertainty regarding the exact number of transfusion episodes given from 7 of the 20 bases due to underreporting of data in their electronic patient journal systems.

In this survey, we described the use of LTOWB in prehospital air ambulance services in Norway. HEMS and blood banks report favorable experiences in the implementation and utilization of LTOWB. We conclude that LTOWB is feasible both from the air ambulance and blood banking perspectives and that LTOWB is preferred by a majority of the HEMS and SAR bases. Our findings support further efforts to enable the implementation of prehospital LTOWB programs.

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Statement of Ethics

This was a survey on the implementation, utilization, and experience with the use of blood products in the HEMS and SAR helicopter services in Norway with a focus on our LTOWB program. The survey was conducted and funded by the Department of Immunology and Transfusion Medicine and the Department of Anesthesia and Intensive Care, Haukeland University Hospital (Bergen, Norway). No information on individual patients was collected. The local data protection officer reviewed the survey.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to *Transfusion Medicine and Hemotherapy*. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Norwegian Armed Forces Medical Services.

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Author Contributions

C.K.B. and T.O.A. designed the survey, performed the data collection, and drafted the manuscript. G.S. contributed in the design of the survey. G.S., T.H., and G.A.S. revised the manuscript critically and contributed to the writing of the manuscript. All authors approved the final version of the manuscript for publication.

References

1 Espinosa A, Dybvik B, Medby C, Vangberg G. Implementation of a protocol for prehospital transfusion of low-titer, leukocyte-depleted whole blood for civilian bleeding patients. Transfus Apher Sci. 2019;58:212–5.
2 Sunde GA, Vikenes B, Strandenes G, Flo KC, Hervig TA, Kristoffersen EK, et al. Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. J Trauma Acute Care Surg. 2015;78:S26–30.
3 Zielinski MD, Stubbs JR, Berns KS, Glassberg E, Murdock AD, Shinar E, et al. Prehospital blood transfusion programs: Capabilities and lessons learned. J Trauma Acute Care Surg. 2017;82:S70–S8.
4 Traumeplan Norge [monograph on the internet]. Available from: https://traumeplan.no/.
5 Cantle PM, Cotton BA. Balanced resuscitation in trauma management. Surg Clin North Am. 2017;97:999–1014.
6 Butler FK, Holcomb JB, Schreiber MA, Kotwal RS, Jenkins DA, Champion HR, et al. Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: TCCC guidelines change 14-01 – 2 June 2014. J Spec Oper Med. 2014;14:13–38.
7 Cap AP, Pidcoke HF, Spinella P, Strandenes G, Borgman MA, Schreiber M, et al. Damage Control Resuscitation. Mil Med. 2018;183:36–43.
8 Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. Transfusion. 2006;46:685–6.
9 Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma. 2007;62:307–10.
10 Spinella PC, Doctor A. Role of transfused red blood cells for shock and coagulopathy within remote damage control resuscitation. Shock. 2014;41(Suppl 1):30–4.
11 Powell EK, Hinckley WR, Gottula A, Hart KW, Lindsell CJ, McMullan JT. Shorter times to packed red blood cell transfusion are associated with decreased risk of death in traumatically injured patients. J Trauma Acute Care Surg. 2016;81:458–62.

12 Brown LM, Call MS, Margaret Knudson M, Cohen MJ, Holcomb JB, Holcomb JB, et al. A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. J Trauma. 2011;71:S337–42.
13 Frith D, Brohi K. The pathophysiology of trauma-induced coagulopathy. Curr Opin Crit Care. 2012;18:631–6.
14 Kutcher ME, Redick BJ, McCreery RC, Crane IM, Greenberg MD, Cachola LM, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg. 2012;73:13–9.
15 Ramsey MT, Fabian TC, Shahan CP, Sharpe JP, Mabry SE, Weinberg JA, et al. A prospective study of platelet function in trauma patients. J Trauma Acute Care Surg. 2016;80:726–3; discussion 32–3.
16 Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, et al. Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma. 2008;64:1211–7; discussion 7.
17 Brohi K, Cole E, Hoffman K. Improving outcomes in the early phases after major trauma. Curr Opin Crit Care. 2011;17:515–9.
18 Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54:1127–30.
19 Bjerkvig CK, Strandenes G, Eliassen HS, Spinella PC, Fosse TK, Cap AP, et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion. 2016;56(Suppl 2):S182–9.
20 Armand R, Hess JR. Treating coagulopathy in trauma patients. Transfus Med Rev. 2003;17:223–31.
21 Norwegian Air Ambulance [monograph on the internet]. Available from: http://www.luftambulanse.no/about-national-air-ambulance-services-norway.
22 The Guide to the preparation, use and quality assurance of blood components [monograph on the internet]. 2017. Available from: https://www.edqm.eu/en/blood-transfusion-guide.
23 Shackelford SA, Del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. JAMA. 2017;318:1581–91.
24 Pusateri AE, Moore EE, Moore HB, Le TD, Guyette FX, Chapman MP, et al. Association of prehospital plasma transfusion with survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials. JAMA Surg. 2020;155:e195085.
25 Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018;379:315–26.
26 Gerhardt RT, Strandenes G, Cap AP, Rentas FJ, Glassberg E, Mott J, et al. Remote damage control resuscitation and the Solstrand Conference: defining the need, the language, and a way forward. Transfusion. 2013;53(Suppl 1):9S–16S.
27 Spinella PC, Strandenes G, Rein EB, Seghatchian J, Hervig T. Symposium on fresh whole blood for severe hemorrhagic shock: from in-hospital to far forward resuscitations. Transfus Apher Sci. 2012;46:113–7.
28 Jenkins DH, Rappold JF, Badloe JF, Berséus O, Blackbourne L, Brohi KH, et al. Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: definitions, current practice, and knowledge gaps. Shock. 2014;41(Suppl 1):3–12.
29 Jackson B, Murphy C, Fontaine MJ. Current state of whole blood transfusion for civilian trauma resuscitation. Transfusion. 2020;60(Suppl 3):S45–52.
30 Yazer MH, Spinella PC, Anto V, Dunbar NM. Survey of group A plasma and low-titer group O whole blood use in trauma resuscitation at adult civilian level 1 trauma centers in the US. Transfusion. 2021;61(6):1757–63.
31 Transfusion Strategies in the Pre-Hospital Setting: Evaluating the Logistical Benefits of Pre-Hospital Whole Blood Transfusion, and a National Survey of Pre-Hospital Blood Transfusion [monograph on the internet]. Available from: https://www.researchgate.net/publication/348614500_Transfusion_Strategies_in_the_Pre-Hospital_Setting_Evaluating_the_Logistical_Benefits_of_Pre-Hospital_Whole_Blood_Transfusion_and_a_National_Survey_of_Pre-Hospital_Blood_Transfusion/fulltext/600787b1a6fdccdcb8689b34/Transfusion-Strategies-in-the-Pre-Hospital-Setting-Evaluating-the-Logistical-Benefits-of-Pre-Hospital-Whole-Blood-Transfusion-and-a-National-Survey-of-Pre-Hospital-Blood-Transfusion.pdf.
32 The Joint Trauma System Tactical Combat Casualty Care (TCCC) Guidelines. 2020 [cited 13 Jul 2021]. Available from: https://www.deployedmedicine.com/content/40.
33 Hunt BJ, Allard S, Keeling D, Norfolk D, Stanworth SJ, Pendry K, et al. A practical guideline for the haematological management of major haemorrhage. Br J Haematol. 2015;170:788–803.
34 Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, Group PS, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313:471–82.
35 Cardenas JC, Zhang X, Fox EE, Cotton BA, Hess JR, Schreiber MA, et al. Platelet transfusions improve hemostasis and survival in a substudy of the prospective, randomized PROPPR trial. Blood Adv. 2018;2:1696–704.
36 Bjerkvig C, Sivertsen J, Braathen H, Lunde THF, Strandenes G, Assmus J, et al. Cold-stored whole blood in a Norwegian emergency helicopter service: an observational study on storage conditions and product quality. Transfusion. 2020;60:1544–51.
37 Yazer MH, Spinella PC. An international survey on the use of low titer group O whole blood for the resuscitation of civilian trauma patients in 2020. Transfusion. 2020;60(Suppl 3):S176–S9.
38 Seheult JN, Anto V, Alarcon LH, Sperry JL, Triulzi DJ, Yazer MH. Clinical outcomes among low-titer group O whole blood recipients compared to recipients of conventional components in civilian trauma resuscitation. Transfusion. 2018;58:1838–45.
39 Yazer MH, Freeman A, Harrold IM, Anto V, Neal MD, Triulzi DJ, et al. Injured recipients of low-titer group O whole blood have similar clinical outcomes compared to recipients of conventional component therapy: A single-center, retrospective study. Transfusion. 2021;61(6):1710–20.
40 Hagen KG, Strandenes G, Kristoffersen E, Braathen H, Sivertsen J, Bjerkvig CK, et al. A whole blood based resuscitation strategy in civilian medical services; experience from a Norwegian hospital in the period 2017–2020. Transfusion. 2021, in press.
41 Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. J Trauma Acute Care Surg. 2016;81:21–6.
42 Sperry J. Pragmatic Prehospital Group O Whole Blood Early Resuscitation (PPOWER) Trial: A Prospective, Interventional, Randomized, 3 Year, Pilot Clinical trial. Bethesda, MD: National Heart, Lung, and Blood Institute (NHLBI); 2018.
43 Sperry JLEB, Buck M, Silfies L. Shock, whole blood and assessment of TBI (SWAT). Pittsburgh, PA: University of Pittsburgh; 2018.
44 Martinaud C, Tiberghien P, Bégué S, Sailliol A, Gross S, Pouget T, et al. Rational and design of the T-STORHM Study: A prospective randomized trial comparing fresh whole blood to blood components for acutely bleeding trauma patients. Transfus Clin Biol. 2019;26:198–201.

IV

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ORIGINAL RESEARCH

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Implementation of a low-titre whole blood transfusion program in a civilian helicopter emergency medical service

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Abstract

Background: Early balanced transfusion is associated with improved outcome in haemorrhagic shock patients. This study describes the implementation and evaluates the safety of a whole blood transfusion program in a civilian helicopter emergency medical service (HEMS).

Methods: This prospective observational study was performed over a 5-year period at HEMS-Bergen, Norway. Patients in haemorrhagic shock receiving out of hospital transfusion of low-titre Group O whole blood (LTOWB) or other blood components were included. Two LTOWB units were produced weekly and rotated to the HEMS for forward storage. The primary endpoints were the number of patients transfused, mechanisms of injury/illness, adverse events and survival rates. Informed consent covered patient pathway from time of emergency interventions to last endpoint and subsequent data handling/storage.

Results: The HEMS responded to 5124 patients. Seventy-two (1.4%) patients received transfusions. Twenty patients (28%) were excluded due to lack of consent (16) or not meeting the inclusion criteria (4). Of the 52 (100%) patients, 48 (92%) received LTOWB, nine (17%) received packed red blood cells (PRBC), and nine (17%) received freeze-dried plasma. Of the forty-six (88%) patients admitted alive to hospital, 35 (76%) received additional blood transfusions during the first 24 h. Categories were blunt trauma 30 (58%), penetrating trauma 7 (13%), and nontrauma 15 (29%). The majority (79%) were male, with a median age of 49 (IQR 27–70) years. No transfusion reactions, serious complications or logistical challenges were reported. Overall, 36 (69%) patients survived 24 h, and 28 (54%) survived 30 days.

Conclusions: Implementing a whole blood transfusion program in civilian HEMS is feasible and safe and the logistics around out of hospital whole blood transfusions are manageable.

Trial registration The study is registered in the ClinicalTrials.gov registry (NCT02784951).

Keywords: Out of hospital, Blood transfusion, Haemorrhagic shock, Helicopter Emergency Medical Services, Low-titre group O whole blood

Introduction

Haemorrhage is a leading cause of early death in trauma patients worldwide, but the optimal haemorrhagic shock resuscitation strategy is still under discussion [1, 2]. Development in military and civilian trauma care over the last decade indicates that crystalloid or colloid-based resuscitation causes haemodilution, acidosis and reduced

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oxygen delivery, suggesting that an early blood-based resuscitation strategy can be superior for treating major haemorrhage in the out of hospital setting [3, 4]. Military use of blood products is a key element in remote damage control resuscitation (RDCR), as it reduces the time to transfusion and improves survival in combat causalities [5].

Recently, some civilian emergency medical services have established systems for whole blood, packed red blood cells (PRBC) and plasma administration [6, 7]. Whole blood shows logistical advantages over a balanced transfusion strategy using PRBC and plasma, is less haemodiluted and contains platelets that improve clotting [8, 9]. Whole blood transfusions may improve shock severity and coagulopathy compared to traditional resuscitation with crystalloid fluids or blood components [10]. Improved survival in civilian trauma patients receiving whole blood in the emergency department has been shown [9].

However, evidence describing out of hospital whole blood use in civilian haemorrhagic shock patients is scarce. In 2015, our helicopter emergency medical service (HEMS) was one of the first civilian physician-staffed services to implement an out of hospital whole blood transfusion program. This study aimed to describe and evaluate the implementation and safety of this transfusion program, with primary endpoints being the number and category of patients transfused, transfusion-related adverse events and 24-h/30-day survival rates.

Methods

Ethical approval

The Regional Committee for Medical and Health Research Ethics in Norway (REK-Vest-2016/304) approved the study. Informed consent covered patient pathway from time of emergency interventions to last endpoint and subsequent data handling/storage. Written informed consent was obtained from surviving subjects and waived for deceased participants. The study is registered in the ClinicalTrials.gov registry (NCT02784951).

Patients

Patients in haemorrhagic shock and receiving out of hospital transfusion of low-titre Group O whole blood (LTOWB) or PRBC were included. Transfusions were done in compliance with HEMS standard operating procedures describing the use of blood products and the accompanying bundle of care (e.g., tranexamic acid, calcium or pelvic binders). Transfusion was initiated at the physician's discretion in patients with a mechanism of injury or illness compatible with active bleeding and in haemorrhagic shock (e.g., penetrating trauma to the torso), absent or elevated radial pulse (above 100 beats per minute), decreased systolic blood pressure (SBP) below 90 mmHg, or altered mental status (reduced Glasgow Coma Scale (GCS)) in the absence of head injury or known intoxication. Exclusion criteria were previous allergic reactions to blood transfusions or refusal of blood products on religious grounds (e.g., Jehovah's Witness).

Conduct of the study

This prospective observational study was performed at HEMS-Bergen over a 5-year period from December 2015 to December 2020. The HEMS is located at the regional trauma centre for the western part of Norway at Haukeland University Hospital in Bergen and is staffed by a physician, flight paramedic, and pilot. All physicians are specialists in anaesthesiology, with a median HEMS experience of 16.5 (IQR 6–19.5) years. The pilots have extensive military or civilian flight experience prior to starting HEMS service, with all-weather/instrument flight/night-vision-goggles capabilities. The flight paramedics are paramedics or nurses, and fulfil national standards for HEMS flight paramedics issued by the Ministry of Justice and Public Security (e.g., education, rescue and medical competence). The HEMS covers a population of approximately 550,000 people across 15,500 km^2, including urban and rural areas, a coastline, several fjords, and high mountains. It operates 24/7/365 and responds by helicopter or rapid response car to medical and trauma cases (ratio 60:40). Data were obtained from patient records. Out of hospital injury severity was classified using the National Advisory Committee on Aeronautics' (NACA) severity score [11]. The study complied with Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines [12].

Endpoints

Primary endpoints were the number and category of patients transfused, transfusion-related adverse events and 24-h/30-day survival rates. Secondary endpoints were key vital signs, HEMS response times and emergency interventions.

Blood products and logistics

LTOWB units are produced weekly at the Department of Immunology and Transfusion Medicine (Haukeland University Hospital, Bergen) and rotated to the HEMS for forward storage at the base [13]. If unused, the units are rotated back and used for a total storage period of up to 21 days. If transfused, they are immediately replaced with LTOWB or freshly produced PRBC (0 Rh (D) negative) units. The LTOWB units are donated by regular blood donors and tested for infectious agents and blood type antibodies in accordance with Norwegian and European legal regulations [14]. The LTOWB is leukocyte reduced

with a platelet-sparing filter (IMUFLEX, WB-SP Blood Bag System, TERUMOBCT, Lakewood, CO, USA). Continuous quality monitoring of used blood products is performed at the Department of Immunology of Transfusion Medicine in accordance with the European recommendations [14]. If needed, additional transfusion with freeze-dried plasma (FDP) (LyoPlas N-w (Deutsches Rotes Kreuz—Blutspendedienst West, Hagen, Germany) may be given. The FDP used is a quarantined single donor plasma. We currently use group AB or A plasma. LyoPlas powder dissolves in 200 ml of sterile water and is ready for injection within 5–10 min depending on water temperature and can be administered intravenously or intraosseously.

The HEMS is deployed with two units of LTOWB and one unit of FDP. The HEMS crew, including flight paramedics and pilots, are trained in administering transfusions of LTOWB, FDP or PRBC on the physician's orders. The LTOWB units are stored in a portable thermal "golden hour box" (Pelican Biothermal, Plymouth, MN, USA). Crēdo Duracube, Series 4 2L HD, 2–8 °C, 272), and the temperature is monitored with a temperature logger. The box is stored in a refrigerator at the HEMS base at 4 °C between missions. We have validated the box to maintain temperature at 4 °C under these conditions for more than a week [7].

Statistics

Continuous variables are expressed as medians with interquartile ranges (IQRs) or means (standard deviations), and categorical variables are expressed as numbers with percentages of the total. The Wilcoxon matched-pairs signed rank test was used when comparing out of hospital and in-hospital vital signs. *P* values less than 0.05 were considered statistically significant. The statistical package for IBM SPSS statistics (SPSS, version 26.0, IBM Corporation, New York, USA) was used for statistical analysis.

Results

Patients

In the 5-year study period, the HEMS responded to 5124 patients. Seventy-two patients received out of hospital LTOWB, FDP or PRBC transfusions from December 2015 to December 2020. Sixteen patients were excluded due to lack of consent, and four patients did not meet the inclusion criteria. We analysed data from the remaining 52 (100%) patients with written consent (Fig. 1: flowchart). The mean NACA score was 5.63 (SD 0.864) (Additional file 1). Patient characteristics are summarized in Table 1, and biochemistry analyses are summarized in Table 2. The main mechanisms of injury in trauma patients were motor vehicle accidents (26.9%) and falls from heights (15.4%). In nontrauma patients, gastrointestinal bleeding (15.4%) and ruptured aortae (9.6%) dominated (Table 3). The overall transfusion rate was 1.4%.

Survival

Overall, 36 (69%) patients survived the first 24 h, and 28 (54%) patients survived 30 days. Of the 24 (46%) deaths in total, six (12%) died within 1 h, an additional seven (13%) within 6 h and three (6%) within 24 h. The remaining eight (15%) died within 30 days. Ten (19%) patients presented with cardiac arrest (CA) on-scene: seven (70%) with blunt trauma, two (20%) with penetrating trauma and one (10%) with nontrauma. Four (40%) patients with initial CA on-scene were admitted with signs of life. However, no patients presenting with CA on-scene survived beyond 24 h.

Transfusion-related adverse events and waste

No clinical transfusion reactions were reported out of hospital or after admission. Furthermore, there were no other serious complications or adverse events related to the transfusion procedure. Each blood unit in the blood bank inventory is electronically supervised from donor to patient by a single blood bank laboratory information system, including those at the HEMS base. No waste of prepared plasma or blood units was recorded at the HEMS due to rotation of the unused units to the in-hospital use at the Department of Immunology and Transfusion Medicine. In 47 (90%) patients, the physicians reported no technical problems with the transfusions. In two (4%) cases, a sternal intraosseous device failed, and transfusion was delayed. In three (6%) other cases, the team experienced missing transfusion sets, difficulties in establishing intravenous access or pain during initial transfusion.

Out of hospital and in-hospital transfusions

Of 52 (100%) patients, 48 (92%) received LTOWB, nine (17%) received PRBC, and nine (17%) received FDP. Twenty-eight (54%) patients were transfused with one unit of LTOWB, and 20 (39%) patients were transfused with two units. Four (8%) interhospital transfers with ruptured aortic aneurysms (3) or intraabdominal bleeding and pelvic fracture (1) received 4–7 units of PRBC and 2–6 units of FDP in addition to two LTOWB units during transfer to the regional trauma centre.

Of the forty-six (88%) patients who were admitted alive to the hospital, 35 (76%) received additional transfusions of whole blood or blood components during the first 24 h; 15 (33%) received LTOWB, 31 (67%) received PRBC, 28 (61%) received thawed fresh frozen plasma (FFP), and 14 (30%) received platelet concentrates. Eleven (24%) patients were not transfused with additional blood

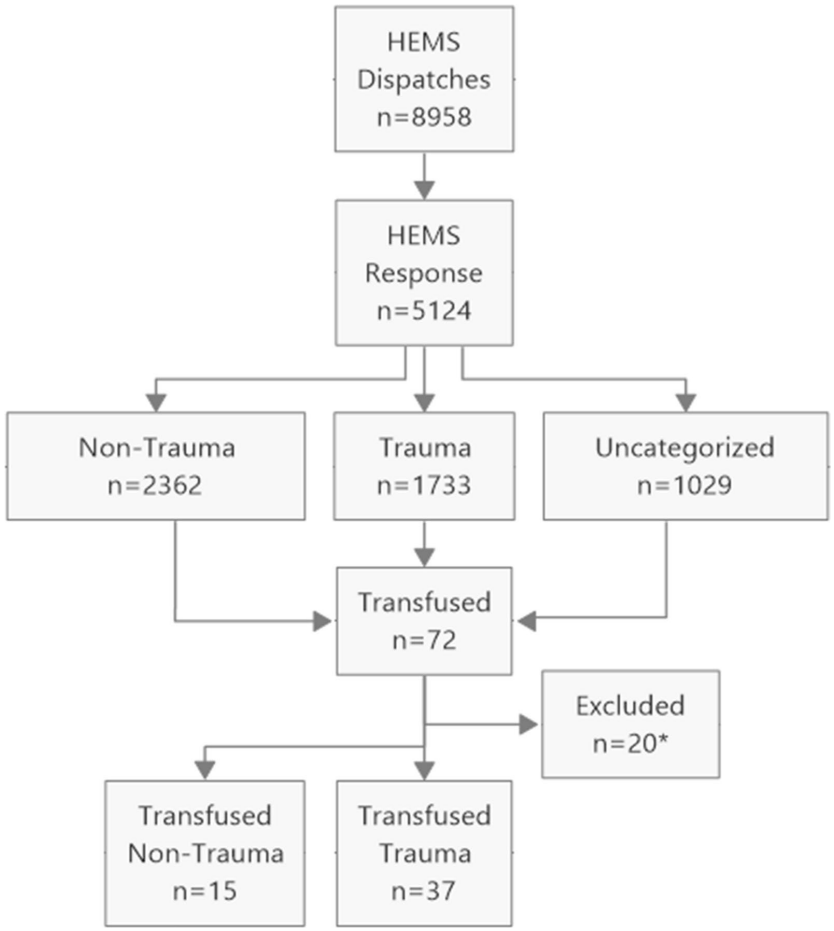

Fig. 1 The flowchart shows the total number of HEMS dispatches and the number of responses by category in the period from December 2015 to December 2020. In total, 72 patients were transfused. *Sixteen patients were excluded due to lack of informed consent, and 4 patients were excluded since they did not meet the inclusion criteria.

products after admission. Out of hospital and in-hospital fluid resuscitation is shown in Table 4. Thirty-three (63%) patients received 1 g of tranexamic acid out of hospital. In the last two years of the study period, calcium chloride was added to the inventory, and four (8%) patients received 5 mmol out of hospital.

Key vital signs

Of the 42 non-CA patients, 24 (57%) had documented blood pressure prior to the start of transfusion. In the non-measured group, three (7%) presented with a palpable peripheral pulse, and ten (24%) presented with a palpable carotid pulse. There were no documented assessment of blood pressure or pulse in five (12%) patients. There were missing data for out of hospital SBP, respiratory rate, and pulse oximetry (SpO_2) in 42%, 10%, and 43% of patients, respectively. Out of hospital and in-hospital vital signs are described (Fig. 2), and significant differences were found for systolic blood pressure, heart rate, and SpO_2.

Table 1 Basic characteristics

Variable	All cases	Trauma	Nontrauma
No. of patients	52 (100)	37 (100)	15 (100)
Male	41 (79)	28 (76)	13 (87)
Age, y	49 (27–70)	41 (21–62)	66 (54–74)
Mission category			
Primary	43 (83)	33 (89)	10 (67)
Secondary	9 (17)	4 (11)	5 (33)
Transport mode			
Ground ambulance	27 (55)	17 (46)	10 (67)
Helicopter	20 (41)	15 (41)	5 (33)
Not transported	2 (4)	2 (5)	0 (0)
NACA score	6 (5–6)	6 (5–6)	6 (5–6)
Timeline			
Response time, min	21 (13–40)	21 (12–37)	25 (14–40)
On-scene time, min	10 (4–20)	11 (4–22)	8 (4–10)
On-scene to hospital arrival, min	20 (13–30)	19 (13–27)	20 (13–36)
Type of injury			
Trauma	37 (71)	37 (100)	0 (0)
Nontrauma	15 (29)	0 (0)	15 (100)
Out of hospital Blood pressure assessment			
Not measured	5 (10)	4 (11)	1 (7)
Central palpable pulse	9 (17)	6 (16)	4 (27)
Peripheral palpable pulse	3 (6)	3 (8)	0 (0)
Measured blood pressure	24 (46)	15 (41)	9 (60)
Cardiac arrest	10 (19)	9 (24)	1 (7)
Airway management			
Endotracheal intubation	15 (29)	13 (35)	2 (13)
Supraglottic device	3 (6)	3 (8)	0 (0)
Mask-bag ventilation	4 (8)	4 (11)	0 (0)
Supplementary oxygen	17 (33)	12 (32)	5 (33)
No airway intervention	13 (25)	5 (14)	8 (53)
Out of hospital			
Systolic blood pressure, mmHg	80 (0–100)	75 (0–98)	97 (50–100)
Heart rate, beats/min	80 (0–100)	65 (0–90)	120 (94–125)
Respiratory rate, breaths/min	13 (0–20)	10 (0–17)	16 (12–28)
Pulse oximetry, %	90.5 (0–99)	84 (0–99)	94 (88–100)
Glasgow coma scale score	9.5 (3–15)	8 (3–15)	12 (3–15)
In-hospital			
Emergency department			
Systolic blood pressure, mmHg	110 (65–130)	110 (76–130)	116 (60–126)
Heart rate, beats/min	94 (70–108)	84 (64–106)	100 (82–113)
Respiratory rate, breaths/min	20 (12–24)	15 (12–24)	22 (16–27)
Pulse oximetry, %	97 (92–100)	98 (88–100)	97 (93–100)
Glasgow coma scale score	12 (3–15)	7 (3–15)	15 (10–15)
Interventions			
Emergency interventions < 24 h	41 (79)	29 (78)	12 (80)
Survival			
Survival 24 h	36 (69)	25 (68)	11 (73)
Survival 30 days	28 (54)	18 (49)	10 (67)

Data are presented as the number of patients (percentage) or median (interquartile range) per patient category

NACA score, National Advisory Committee for Aeronautics score

Table 2 First biochemistry analyses in-hospital (N = 52)

Patients transfused	Number of patients (%)	Values
Haemoglobin (g/dl)	42 (80)	12.9 (11.5–14.1)
Haematocrit	4 (7)	0.30 (0.3–0.4)
INR	25 (48)	1.1 (1.1–1.2)
APTT	24 (46)	33.5 (31–39)
Fibrinogen (g/L)	23 (44)	2.4 (1.8–3.1)
pH	39 (75)	7.3 (7.2–7.4)
Lactate (mmol/L)	39 (75)	4.4 (2.0–10.1)
Base excess	39 (75)	− 5.7 (− 15.7–(− 1.1))
paO_2	39 (75)	22.7 (10.8–36.6)
$paCO_2$	39 (75)	5.4 (4.3–6.4)
Ionized calcium	38 (73)	1.10 (1.0–1.2)

Data are presented as the number of patients (percentage) or median (interquartile range)

APTT, activated partial thromboplastin time; INR, international normalized ratio

Table 3 Mechanisms of injury or illness

Mechanisms of injury or illness	Number of patients	%
Avalanche	1	1.9
Cardiac tamponade	1	1.9
Chainsaw injury	1	1.9
Extremity injury	1	1.9
Epistaxis	1	1.9
Fall from heights- multitrauma	8	15.4
Gastrointestinal bleeding	8	15.4
Gunshot wounds- multitrauma	2	3.8
Motor vehicle accident- multitrauma	14	26.9
Ruptured aorta	5	9.6
Stab injuries- multitrauma	4	7.7
Surgical complications	1	1.9
Traumatic brain injury	1	1.9
Vehicle versus pedestrian accident	2	3.8
Wind-thrown tree	2	3.8
Total	52	100.0

Table 4 Out of hospital and in-hospital volume replacement

Variable	Number of patients (%)	Volume replacement
Out of hospital		
Clear fluids, ml	9 (17)	716 (606)
Red blood cells, units	9 (17)	3.33 (2.35)
Plasma, units	9 (17)	1.78 (1.64)
Whole blood, units	48 (92)	1.42 (0.51)
In-hospital, < 24 h		
Clear fluids, ml	37 (90)	2007 (1345)
Red blood cells, units	28 (67)	7.39 (11.99)
Plasma, units	25 (60)	8.36 (14.60)
Platelets, units	13 (32)	3.36 (5.05)
Whole blood, units	14 (34)	7.60 (7.89)

Data are presented as the number of patients (percentage) or mean (standard deviation)

Airway management

All 10 (19%) patients presenting with CA received advanced airway management. Of these, six (60%) received endotracheal intubation (ETI), three (30%) received a supraglottic airway device, and one (10%) received bag-mask-ventilation. Excluding CA patients, nine (21%) received rapid sequence induction and ETI, three (7%) received bag-mask ventilation, 17 (40%) received supplemental oxygen on a nonrebreather mask, and 13 (31%) received no advanced airway interventions.

Response and transport times

The response, on-scene and transport times are presented in Table 1. The median response time was 20 min (IQR 12–35) on primary missions, 37 min (IQR 20–43) on secondary missions, and 21 min on cardiac arrest missions (IQR 10–43). The median "on-scene-time" was 7.5 min (IQR 4–19), 15 min (IQR 9–24), and 14 min

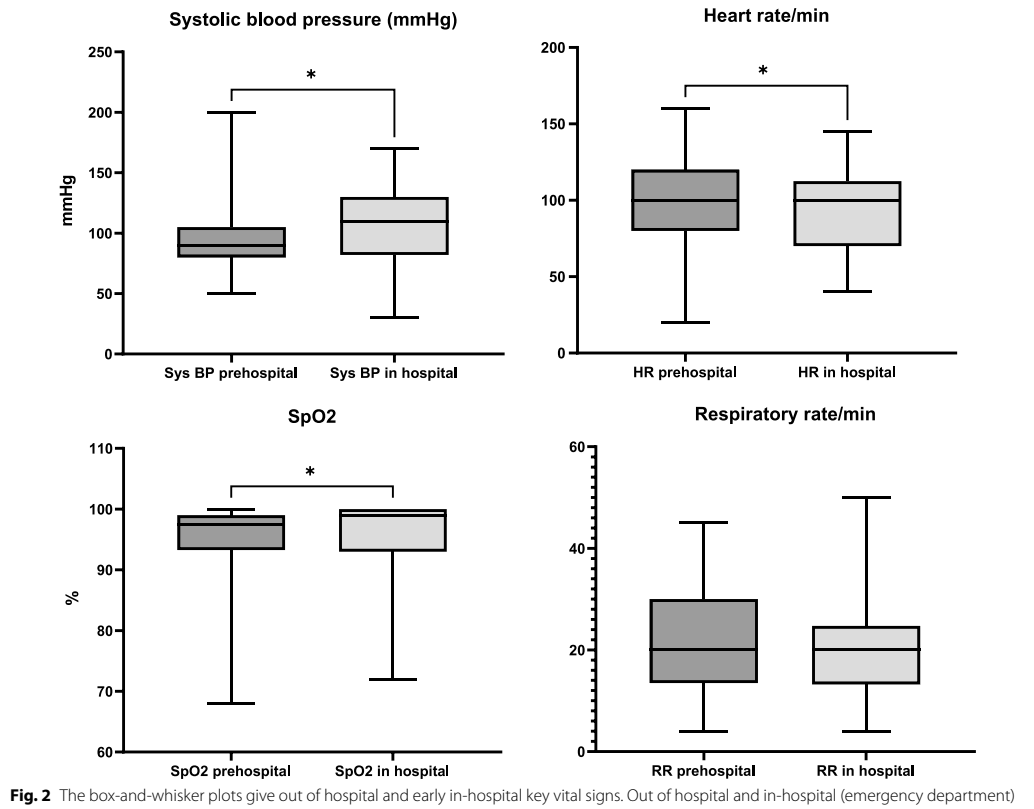

Fig. 2 The box-and-whisker plots give out of hospital and early in-hospital key vital signs. Out of hospital and in-hospital (emergency department) values were compared using the Wilcoxon matched-pairs signed rank test, and significant *p* values were found for systolic blood pressure (SBP) ($p = 0.0169$), heart rate ($p = 0.0169$), and SpO_2 ($p = 0.0242$). Patients with cardiac arrest were excluded from the analysis

(IQR 3–28), respectively. The median transport time was 19 min for primary missions (IQR 12–26), 35 min for secondary missions (IQR 20–41), and 20 min for cardiac arrest missions (IQR 12–38).

Implementation process

Prior to implementation of the LTOWB transfusion program, over 30 units were subjected to extensive in vitro quality control analysis. As LTOWB is not an ordinary blood product in Norway, we applied to the appropriate regulatory body and were granted permission to use LTOWB in out of hospital emergencies. For the first two years of the program, the returned LTOWB units were subjected to internal quality controls (e.g., haemolysis at the end of storage) and then discarded. In December 2017, usage of LTOWB was implemented for in-hospital massive transfusion protocols. Subsequently, all returned LTOWB units were incorporated into the blood bank inventory for in-hospital use or stored for 21 days.

Emergency interventions

In 41 of 46 admitted patients, emergency surgery (e.g., thoracotomy, laparotomy, or craniotomy) or other haemostatic interventions (e.g., sutures of skin or soft tissue lacerations, radiological interventions, bone fracture repairs and gastroscopies) were performed within the first 24 h (Table 1).

Discussion

To our knowledge, this is the first study describing an out of hospital transfusion program with whole blood to patients in haemorrhagic shock by civilian physician-staffed HEMS in Europe. We found that the majority of exsanguination deaths occurred early and within 6 h. Overall, one in three patients receiving transfusion died within 24 h, and only one in two patients survived beyond 30 days, emphasizing the life-threatening nature of their injury or illness and the need to improve out of hospital treatment of civilian patients suffering noncompressible haemorrhage. Our results indicate a restrictive transfusion practice with an overall transfusion rate of 1.4%, comparable to transfusion rates in other air ambulance services (UK) that show approximately 3% in trauma patients receiving PRBC [15]. We found no serious complications or adverse events with whole blood during transfusion or transit. Although logistics around forward storage and transfusion of blood products in the out of hospital setting may be challenging, no adverse or logistical issues were reported. The demographics in our study are comparable with other studies describing out of hospital use of blood products in civilian trauma services, with middle-aged male patients and blunt trauma mechanisms dominating; however, our results cannot compare directly with those from studies describing military use of blood products in younger patients with combat injuries [2, 16].

The main priorities in haemostatic resuscitation are, nonetheless, to stop compressible bleeding, maintain vital organ perfusion and support haemostasis [17]. Although overall trauma mortality has decreased over the last decades due to improved trauma services and hospital infrastructure, most early deaths due to haemorrhage still occur in the pre-surgical phase [18, 19]. The use of out of hospital blood products has evolved to improve the survival of haemorrhaging patients in the field, both civilian and military [10].

Military use of whole blood has become a key element in RDCR, due to simpler logistics, reduced time to transfusion, and improved survival in combat causalities [5, 20]. Whole blood may have better global haemostasis effects, a reduced incidence of transfusion hypocalcaemia and haemodilution, and a reduction in overall blood use compared to components with higher citrate and additives contents [4, 21]. A growing body of evidence supports the use of whole blood for civilian out of hospital patients with noncompressible bleeding [9, 22]. Learning from military experiences, some civilian ambulance services (USA) have recently implemented whole blood programs with success, while the majority still deploy traditional PRBC, FDP or crystalloids [23, 24]. A recent review of air ambulance services (UK) showed that less than half of the services deployed with blood products (PRBC or FFP) [15].

For haemorrhaging patients in extremis to survive, they should have access to modern haemorrhage control treatments available in trauma hospitals as well as balanced blood transfusions [10, 25]. Tailored treatment offering out of hospital whole blood to patients with life-threatening noncompressible haemorrhage may offer a more targeted approach than traditional transfusion protocols [9, 26]. The decision to initiate transfusion in a patient with suspected haemorrhagic shock is both complex and time-critical and is based on a variety of symptoms, clinical presentations and mechanisms of injury. In patients presenting with unstable physiology or clinical signs on scene, a certain degree of overtransfusion may be inevitable [27]. Although increased survival to hospital in trauma patients receiving out of hospital transfusion of PRBC has been shown, this does not necessarily translate into increased long-term survival [28].

Out of hospital resuscitative interventions are often initiated before the cause of hypotension or hypoxia is clearly identified [29]. In our study, SBP was not consistently documented prior to resuscitation, as only approximately half of the patients had a blood pressure reading prior to transfusion. Hence, SBP was not used

as a transfusion trigger in the majority of the patients. In exsanguinating patients, establishing vascular access by intraosseous or intravenous routes to enable transfusion is just one of many timely interventions that must be provided [30]. Therefore, having to prioritize resuscitative efforts before measurements may indicate the degree of haemodynamic instability in these patients and the haste involved in correcting circulatory failure [31]. As the pathophysiology behind hypotension is diverse, it is important that vital signs are interpreted along with clinical symptoms and mechanism of injury or illness by competent providers' on-scene [32]. Having experienced physicians in the HEMS teams may ensure that life-saving interventions can be performed to the same standards as in-hospital emergency treatment without compromising on-scene times [33].

Drug-assisted rapid sequence induction and intubation is the definitive method of securing the airway in trauma patients [34]. The decision whether to intubate patients in haemorrhagic shock may be challenging. The timing of intubation is crucial, and despite current European guidelines, ETI on-scene is not always done [35]. ETI should be restricted to those showing signs of increasing airway compromise or deteriorating level of consciousness [25]. Detrimental effects of advanced airway management strategies in exsanguinating patients have been reported [36]. The physiological effects of ETI and subsequent positive pressure ventilation on venous return may mimic the physiology of tension pneumothorax in hypovolemic patients, leading to a further decrease in cardiac output [37, 38]. Therefore, in patients with non-compressible haemorrhage, reducing on-scene times and postponing ETI until haemorrhage control is achieved may increase survival [25]. Knowledge of whether, when and how to intubate these patients is important [39].

An out of hospital balanced transfusion approach with components is challenging due to different storage conditions for PRBCs, plasma and platelets. Whole blood represents an alternative that is logistically superior and easier to handle in time-critical emergencies with short on-scene and flight times compared to blood components [20]. The production of a leukocyte-reduced, platelet-containing LTOWB unit in our blood bank also requires fewer logistical steps compared to a unit of PRBC concentrate. This whole blood fulfils all quality control parameters detailed in national requirements as well as the European Guidelines concerning testing for infectious agents, haemolysis, and leukocyte depletion [14]. Our system, where unused units are returned and incorporated into the blood bank inventory for further in-hospital use, minimizes potential waste.

The strength of our study is the prospective design involving experienced physicians in charge of patient treatment and data registration and the inclusion of 52 patients in haemorrhagic shock receiving out of hospital blood transfusions over a 5-year study period. The limitations are the small number of patients reflecting the low frequency of haemorrhagic shock in our area of operations and the selection bias represented by the excluded patients. Our patient cohort was also a heterogeneous mix of trauma and nontrauma patients, with different mechanisms of injuries/illnesses and high mortality rates. The ethical committee required written informed consent from all surviving participants. Unfortunately, this was not possible to achieve in sixteen patients. The excluded patients did not differ significantly from the included patients regarding demographics or mechanisms of injury/illness, and we found the study patients to be representative of the target population. Therefore, this selection bias may be of less importance in regard to interpreting our results.

Patients in extremis who require immediate out of hospital blood transfusions are rare, but prospective observational trials can contribute to the overall evidence in this field [40]. More studies are needed to clarify the role of whole blood in civilian out of hospital haemostatic resuscitation and whether early transfusions reduce the overall use of blood products in these patients, as well as aid in developing more objective transfusion protocols. The experience and research gained from the implementation of advanced interventions, such as whole blood transfusion programs in HEMS, may provide guidance on future resuscitation strategies for these patients [25].

Conclusions

Our results indicate that implementing a whole blood transfusion program in civilian HEMS is feasible and safe and that the logistics around out of hospital whole blood transfusions are manageable.

Abbreviations

RDCR: Remote damage control resuscitation; PRBC: Packed red blood cells; HEMS: Helicopter emergency medical service; LTOWB: Low-titre Group O whole blood; SBP: Systolic blood pressure; GCS: Glasgow Coma Scale; NACA: The National Advisory Committee on Aeronautics severity score; FDP: Freeze-dried plasma; IQR: Interquartile ranges; CA: Cardiac arrest; FFP: Fresh frozen plasma; SpO_2: Pulse oximetry; ETI: Endotracheal intubation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13049-022-01051-z.

Additional file 1. Patient NACA score.

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Author contributions
Study concept: GAS, CB, MB, EKK, J-KH. Patient recruitment: GAS, CB, MB, J-KH. Data collection: GAS, CB, MB, J-KH. Data analysis and interpretation: GAS, CB, MB, EKK, GS, ØB, TOA, J-KH. Statistical analysis: GAS, CB, ØB. Drafting of the first manuscript: GAS, CB, MB, EKK, GS, ØB, TOA, J-KH. Revision of the final manuscript: GAS, CB, MB, EKK, GS, ØB, TOA, J-KH. All authors have read and approved the manuscript.

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Availability of data and materials
All data analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
The Regional Committee for Medical and Health Research Ethics in Norway (REK-Vest-2016/304) approved the study. Written informed consent was obtained from surviving subjects and waived for deceased participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. McCullough AL, Haycock JC, Forward DP, Moran CG II. Major trauma networks in England. Br J Anaesth. 2014;113(2):202–6.
2. Crombie N, Doughty HA, Bishop JRB, Desai A, Dixon EF, Hancox JM, et al. Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Haematol. 2022;9:e250–61.
3. Woolley T, Round JA, Ingram M. Global lessons: developing military trauma care and lessons for civilian practice. Br J Anaesth. 2017;119(suppl_1):i135–42.
4. Spinella PC, Gurney J, Yazer MH. Low titer group O whole blood for prehospital hemorrhagic shock: it is an offer we cannot refuse. Transfusion. 2019;59(7):2177–9.
5. Shackelford SA, Del Junco DJ, Powell-Dunford N, Mazuchowski EL, Howard JT, Kotwal RS, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in afghanistan with acute and 30-day survival. JAMA. 2017;318(16):1581–91.
6. Bodnar D, Rashford S, Williams S, Enraght-Moony E, Parker L, Clarke B. The feasibility of civilian prehospital trauma teams carrying and administering packed red blood cells. Emerg Med J. 2014;31(2):93–5.
7. Bjerkvig C, Sivertsen J, Braathen H, Lunde THF, Strandenes G, Assmus J, et al. Cold-stored whole blood in a Norwegian emergency helicopter service: an observational study on storage conditions and product quality. Transfusion. 2020;60(7):1544–51.
8. Seheult JN, Bahr M, Anto V, Alarcon LH, Corcos A, Sperry JL, et al. Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients. Transfusion. 2018;58:2280–8.
9. Hazelton JP, Ssentongo AE, Oh JS, Ssentongo P, Seamon MJ, Byrne JP, et al. Use of cold-stored whole blood is associated with improved mortality in hemostatic resuscitation of major bleeding: a multicenter study. Ann Surg. 2022;276:579–88.
10. Rangrass G. Whole blood use in trauma resuscitation: targeting prehospital transfusion. Curr Opin Anaesthesiol. 2022;35(2):146–9.
11. Raatiniemi L, Mikkelsen K, Fredriksen K, Wisborg T. Do pre-hospital anaesthesiologists reliably predict mortality using the NACA severity score? A retrospective cohort study. Acta Anaesthesiol Scand. 2013;57(10):1253–9.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806–8.
13. Hagen KG, Strandenes G, Kristoffersen EK, Braathen H, Sivertsen J, Bjerkvig CK, et al. A whole blood based resuscitation strategy in civilian medical services: experience from a Norwegian hospital in the period 2017–2020. Transfusion. 2021;61(Suppl 1):S22–31.
14. European Directorate for the Quality of Medicines & HealthCare (EDQM CoE). Guide to the preparation, use and quality assurance of blood components. https://www.edqm.eu/en/blood-transfusion-guide (2017).
15. Naumann DN, Hancox JM, Raitt J, Smith IM, Crombie N, Doughty H, et al. What fluids are given during air ambulance treatment of patients with trauma in the UK, and what might this mean for the future? Results from the RESCUER observational cohort study. BMJ Open. 2018;8(1):e019627.
16. Gurney J, Staudt A, Cap A, Shackelford S, Mann-Salinas E, Le T, et al. Improved survival in critically injured combat casualties treated with fresh whole blood by forward surgical teams in Afghanistan. Transfusion. 2020;60(Suppl 3):S180–8.
17. Kovacs G, Sowers N. Airway management in Trauma. Emerg Med Clin N Am. 2018;36(1):61–84.
18. de Knegt C, Meylaerts SA, Leenen LP. Applicability of the trimodal distribution of trauma deaths in a Level I trauma centre in the Netherlands with a population of mainly blunt trauma. Injury. 2008;39(9):993–1000.
19. Chalkley D, Cheung G, Walsh M, Tai N. Deaths from trauma in London–a single centre experience. Emerg Med J. 2011;28(4):305–9.
20. Levin D, Zur M, Shinar E, Moshe T, Tsur AM, Nadler R, et al. Low-titer group o whole-blood resuscitation in the prehospital setting in Israel: review of the first 2.5 years' experience. Transfus Med Hemother. 2021;48(6):342–9.
21. Kornblith LZ, Howard BM, Cheung CK, Dayter Y, Pandey S, Busch MP, et al. The whole is greater than the sum of its parts: hemostatic profiles of whole blood variants. J Trauma Acute Care Surg. 2014;77(6):818–27.
22. Braverman MA, Smith A, Pokorny D, Axtman B, Shahan CP, Barry L, et al. Prehospital whole blood reduces early mortality in patients with hemorrhagic shock. Transfusion. 2021;61(Suppl 1):S15–21.
23. Brill JB, Tang B, Hatton G, Mueck KM, McCoy CC, Kao LS, et al. Impact of incorporating whole blood into hemorrhagic shock resuscitation: analysis of 1,377 consecutive trauma patients receiving emergency-release uncrossmatched blood products. J Am Coll Surg. 2022;234(4):408–18.
24. Selleng K, Baschin M, Henkel B, Jenichen G, Thies KC, Rudolph M, et al. Blood product supply for a helicopter emergency medical service. Transfus Med Hemother. 2021;48(6):332–41.
25. Ter Avest E, Carenzo L, Lendrum RA, Christian MD, Lyon RM, Coniglio C, et al. Advanced interventions in the pre-hospital resuscitation of patients with non-compressible haemorrhage after penetrating injuries. Crit Care. 2022;26(1):184.
26. Hofer S, Schlimp CJ, Casu S, Grouzi E. Management of coagulopathy in bleeding patients. J Clin Med. 2021;11(1):1.
27. Gavrilovski M, Griggs JE, Ter Avest E, Lyon RM. The contribution of helicopter emergency medical services in the pre-hospital care of penetrating torso injuries in a semi-rural setting. Scand J Trauma Resusc Emerg Med. 2021;29(1):112.

28. Rehn M, Weaver A, Brohi K, Eshelby S, Green L, Roislien J, et al. Effect of pre-hospital red blood cell transfusion on mortality and time of death in civilian trauma patients. Shock. 2018;51:284–8.
29. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–34.
30. Sorgjerd R, Sunde GA, Heltne JK. Comparison of two different intraosseous access methods in a physician-staffed helicopter emergency medical service: a quality assurance study. Scand J Trauma Resusc Emerg Med. 2019;27(1):15.
31. Bjerkvig CK, Strandenes G, Eliassen HS, Spinella PC, Fosse TK, Cap AP, et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion. 2016;56(Suppl 2):S182–9.
32. Seymour CW, Cooke CR, Heckbert SR, Copass MK, Yealy DM, Spertus JA, et al. Prehospital systolic blood pressure thresholds: a community-based outcomes study. Acad Emerg Med. 2013;20(6):597–604.
33. Lockey DJ, Crewdson K, Davies G, Jenkins B, Klein J, Laird C, et al. AAGBI: safer pre-hospital anaesthesia 2017: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia. 2017;72(3):379–90.
34. NICE. Major trauma: assessment and initial management [NG39]. https://www.nice.org.uk/guidance/ng39 (2016).
35. Stausberg T, Ahnert T, Thouet B, Lefering R, Bohmer A, Brockamp T, et al. Endotracheal intubation in trauma patients with isolated shock: universally recommended but rarely performed. Eur J Trauma Emerg Surg Off Publ Eur Trauma Soc. 2022. https://doi.org/10.1007/s00068-022-01988-x.
36. Crewdson K, Rehn M, Brohi K, Lockey DJ. Pre-hospital emergency anaesthesia in awake hypotensive trauma patients: beneficial or detrimental? Acta Anaesthesiol Scand. 2018;62(4):504–14.
37. Funk DJ, Jacobsohn E, Kumar A. Role of the venous return in critical illness and shock: part II-shock and mechanical ventilation. Crit Care Med. 2013;41(2):573–9.
38. Shafi S, Gentilello L. Pre-hospital endotracheal intubation and positive pressure ventilation is associated with hypotension and decreased survival in hypovolemic trauma patients: an analysis of the National Trauma Data Bank. J Trauma. 2005;59(5):1140–5 (**discussion 5–7**).
39. Lockey DJ, Crewdson K, Lossius HM. Pre-hospital anaesthesia: the same but different. Br J Anaesth. 2014;113(2):211–9.
40. Shea SM, Staudt AM, Thomas KA, Schuerer D, Mielke JE, Folkerts D, et al. The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage. Transfusion. 2020;60(Suppl 3):S2–9.

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