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Effectiveness of interventions for emergency care of hypoglycaemia and diabetic ketoacidosis: A systematic review

Jasmine Maharjan [a,*], Sagar Pandit [a], Kjell Arne Johansson [b], Pratik Khanal [b], Biraj Karmacharya [b,c], Gunjeet Kaur [b], Krishna Kumar Aryal [b]

[a] Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Norway
[b] Bergen Centre for Ethics and Priority Setting in Health (BCEPS), Department of Global Public Health and Primary Care, University of Bergen, Norway
[c] Kathmandu University, School of Medical Sciences, Kathmandu University, Nepal

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ABSTRACT

Aim: This systematic review aims to provide evidence on effectiveness of interventions used in emergency care of hypoglycaemia and diabetic ketoacidosis (DKA).

Methodology: This is a systematic review of randomized controlled trials and analytical studies. We selected studies based on eligibility criteria. The databases Medline, Cochrane library and Embase were searched from their inception till November 2, 2022, using search strategy. We used the term such as "diabetes mellitus", "treatment", "hypoglycaemia", "diabetic ketoacidosis", "low blood sugar", "high blood sugar" and Mesh terms like "disease management", "hypoglycaemia", "diabetic ketoacidosis", and "diabetes mellitus" to form search strategy.

Results: Hypoglycemia: Both 10 % dextrose (D10) and 50 % dextrose (D50) are effective options with similar hospital mortality D10 (4.7 %) and D50 (6.2 %). *DKA:* Low dose insulin is non-inferior to standard dose with time till resolution of DKA 16.5 (7.2) hours and 17.2 (7.7) hours (p value = 0.73) respectively. In children, subcutaneous insulin was associated with reduced ICU admissions and hospital readmissions (67.8 % to 27.9 %). Plasmalyte (PL) is noninferior to sodium chloride (SC), with ICU length of stay 49 h (IQR 23–72) and 55 h (IQR 41–80) respectively, hyperchloremia was associated with longer in-hospital length of stay and longer time to resolution of DKA. And potassium replacement at < 10 mmol/L was associated with higher mortality (n = 72).

Conclusion: We conclude either of the 10 % or 50 % dextrose is effective for management of hypoglycaemia. For DKA subcutaneous insulin and intravenous insulin, chloride levels ≤ 109 mEq/L, potassium above 10 mmol/l, IV fluids like Plasmalyte and normal saline are effective.

1. Introduction

Hypoglycaemia and hyperglycaemic crises are the most common acute complications in patients with diabetes mellitus (DM) [1]. According to the World Health Organization (WHO), hypoglycaemia is defined as a plasma blood glucose level ≤ 3.9 mmol/l (70 mg/dl) [2,3]. Hypoglycaemia is a preventable cause of mortality, morbidity and impaired quality of life [2]. It is more common among older adults, with the risk of developing hypoglycaemia doubling after the age of 60 years [4]. Hypoglycaemia is associated with two to three folds increase in mortality rates with increasing age and history of previous severe hypoglycaemia [1,5].

Hyperglycaemia is a life-threatening condition and is categorized into two conditions based on their different biochemical features: diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). The WHO defines DKA as plasma glucose level ≥ 13.9 mmol/l (250 mg/dl) with urine ketone present in biochemical examination of urine sample [3]. DKA is a most serious hyperglycaemic emergency in patients with type 1 and type 2 DM [6]. It is also a leading cause of mortality among young children and adults with type 1 DM [1,7]. DKA accounts for about 50 % death in young children and adults with type 1 DM, however the mortality rates are higher among older adults (>60 years) and people with life threatening illness [1].

According to the WHO and American diabetes association (ADA) guidelines for management of diabetes complications [3,8], hypoglycaemia can be managed by ingestions of any form of carbohydrate if

* Corresponding author.
E-mail address: jasminemaharjan883@gmail.com (J. Maharjan).

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the patient is capable of drinking or swallowing. For unconscious patients WHO recommends intravenous (IV) administration of glucose. Whereas ADA recommends use of glucagon for treatment of moderate to severe hypoglycaemia.

For management of DKA both ADA and WHO recommends referral of all suspected cases to the hospital, correction of dehydration, intravenous rehydration by infusion of isotonic saline and correction of electrolyte imbalance like potassium. According to the updated guideline revised by joint British diabetes societies for inpatient care (JBDS-IP) [9], recommendations for DKA management are reducing rate of insulin infusion to 0.05 units/kg/hr. If glucose level drops to $<$ 14 mmol/l and the glucose lowering should be at least 3.0 mmol/hr. For fluid resuscitation crystalloid solutions are recommended, and 0.9 % sodium chloride is the fluid of choice. Routinely bicarbonate and phosphate administration are not recommended.

During scoping review of the interventions listed in disease control priorities- third edition (DCP-3) [10], as well as WHO- universal health coverage (UHC) compendium [11] we identified a knowledge gap related to the management of acute complications in DM. The existing literatures does not include studies on all the interventions used for management, also the management guidelines formulated is not based on systematic reviews. The management strategies for acute hypoglycaemia and DKA are optimal in high income countries (HIC) despite that there are variations within the guidelines across hospitals [12]. Whereas, in lower income countries (LICs) and lower- and middle-income countries (LMICs), there is lack of policy guidelines for effective management of acute hypoglycaemia and DKA [13,14].

The lack of optimal management strategy such as lack of provision of continuous blood glucose monitoring, poor adherence to insulin therapy, poor access to care, infections, newly diagnosis of DM [1] result in increase in prevalence of DKA and hypoglycaemia. Similarly, conditions like insulin pump failure, fasting, surgeries can cause euglycemic DKA. It is a condition in which DKA is developed with no elevation of blood glucose in patients with diabetes. The conditions like DKA and hypoglycaemic episodes are critical and requires medical attention globally. As there is lack of systematic review acknowledging effectiveness of all interventions recommended by WHO-UHC compendium on both hypoglycaemia and DKA, we ought to conduct a comprehensive systematic review on the effectiveness of emergency care used to manage hypoglycaemia and DKA. Also, lack of systematic reviews undermines the establishment of standardized and evidence-based approaches. It may lead to inconsistencies in management of acute complications of diabetes and hinder optimal care for individuals experiencing these acute complications [13,14]. This situation poses an increasing risk of mortality, disability, and decreased quality of life, especially in low-and middle- income countries (LMICs). A comprehensive systematic review would help improvise the management guidelines of these two critical emergencies, and hence we aimed to identify effectiveness of interventions on both hypoglycaemia and DKA based on mortality, disability adjusted life years and quality adjusted life years. This systematic review expects to fill the knowledge gap by providing empirical evidence on the management of acute complications in DM. The findings from the review can guide policy makers in designing a national health benefit package (HBP), developing clinical guidelines, and selecting appropriate interventions in emergency care that would improve health outcomes for individuals with DM. The overall aim of this systematic review is to provide evidence on effectiveness of interventions used in emergency care of hypoglycaemia and DKA. This systematic review will only focus on DKA.

2. Methods

This systematic review is reported based on preferred reporting items for systematic reviews and *meta*-analyses (PRISMA) checklist [15] and guided by Cochrane handbook for systematic reviews of interventions [16]. The review protocol was registered in international prospective register of systematic reviews (PROSPERO), with identification number CRD42022367722 and title “effects of management of acute hypoglycaemia and diabetic ketoacidosis in diabetes mellitus: a systematic review”.

2.1. Eligibility criteria

We adopted population, intervention, and outcomes (PIO) framework to structure the eligibility criteria for this systematic review. This review included studies focusing on the effectiveness of different interventions in DM patients with hypoglycaemia and DKA. The study eligibility determined by PIO is elaborated in Table 1. For both hypoglycaemia and DKA, we did not specify comparators for the search strategy to prevent narrowing of search results. Eligibility of the study was also determined by study design, language, and type of diabetes. We only included studies published in English language; randomized controlled trials (RCTs); cluster randomized controlled trials; cohort studies and case control studies. We included people with type 1 and type 2 DM. We excluded studies with gestational diabetes mellitus (GDM), diabetes insipidus and metabolic syndrome. Studies with metabolic syndrome were excluded because we wanted to study people with diabetes and people with metabolic syndrome have hyperglycaemia as a key feature, with or without diabetes mellitus [17].

2.2. Information sources and searches

The search strategy was developed with the help of an information specialist from the Library in University of Bergen. The electronic health databases namely Medline, Embase and Cochrane library were searched for relevant literatures from their inception till November 2, 2022. We also searched for the reference list of systematic reviews and treatment guidelines identified during screening process. The search strategy was made with a combination of medical subject heading (Mesh) terms and text words with Boolean operators firstly, for a database and then, adapted to other databases. We used the term such as “diabetes mellitus”, “treatment”, “hypoglycaemia”, “diabetic ketoacidosis”, “low blood sugar”, “high blood sugar” and Mesh terms like “disease management”, “hypoglycaemia”, “diabetic ketoacidosis”, and “diabetes mellitus” to form search strategy. The search strategy used for this review is elaborated in annex 2 (in supplementary file 1). After completing the final search, we decided to add QALYs as an outcome measure supplementary search focused on QALYs was then conducted which is elaborated in annex 3 (in supplementary file 1).

Table 1
Table showing PIO for hypoglycemia and DKA.

PIO	Hypoglycemia	DKA
Population	Blood glucose level of $\leq$ 3.9 mmol/l (70 mg/dl) in people with type 1 or type 2 DM	Blood glucose level of $\geq$ 13.9 mmol/l (250 mg/dl) with urine ketones present in people with type 1 or type 2 DM
Interventions	Management of hypoglycemia (oral glucose or carbohydrates or intravenous glucose or intravenous dextrose)	Management of DKA (insulin, intravenous fluids, electrolytes)
Outcomes	Mortality, disability adjusted life years (DALYs), quality adjusted life years (QALYs)	Mortality, DALYs, QALYs

2.3. Selection of studies

The records from different electronic databases were combined in EndNote version 20 [18] and duplicate records were removed. The combined results from databases were then imported to Rayyan, a web-based program [19] where any remaining duplicates were automatically removed. Two independent reviewers (JM and SP) were responsible for screening. The screening process was conducted in two steps, we first conducted title/abstract screening followed by full text screening by two independent reviewers. The review meetings were organised after completion of every step until the end of full text screening. The screening was done based on eligibility criteria, most of the studies were excluded for having different population, interventions, study designs or outcomes. Any disagreement that arose between the reviewers at any step during the screening process were resolved through discussions with experts (KAJ, KA and PK).

2.4. Data extraction process and quality assessment

Data extraction was carried out by two reviewers, with JM responsible for extracting data and SP tasked with verifying for completeness and accuracy of the extracted data. If there were any disagreements between the reviewers, an expert (KA) was consulted. The adapted version of Cochrane data extraction form for RCTs and non-randomized studies (NRS) was used to extract data. The adaptation involved expanding more sections of the form to accommodate specific requirements. The form was piloted before actual data extraction to ensure its effectiveness. The collected data on study design, patient characteristics, settings, intervention, and outcomes were extracted and compiled in Microsoft excel version 2013.

Two reviewers (JM and SP) independently assessed the quality of each included study, any disagreements in the process were solved by discussion or by consulting expert (KA). For parallel and cluster randomized trials, a revised Cochrane risk of bias tool (RoB2) [23] was used. As the design of cluster randomized control trials have distinct design considerations, a different version of RoB2, RoB2 CRT [24] was used. The RoB2 tool has fixed five sets of domains focusing on different aspects of trial design, conduct and reporting. Quality assessment involved answering specific signalling questions and following an algorithm to make judgements. The signalling questions were answered using categories as yes, probably yes, no, probably no or no information, the algorithms then led into an overall judgment as high risk, some concerns and low risk of bias [23]. The five domains in RoB2 were: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcome and bias in selection of reported result. When the signalling questions were answered in the tool, a risk of bias graph was obtained following an algorithm.

The New-castle Ottawa scale (NOS) [25] was used for quality assessment of cohort studies. The quality of study was assessed based on selection of study groups, the comparability of groups and the ascertainment of either exposure or outcome. The overall quality of study was determined by a star-based scoring system, a study was given one star for each numbered item in selection and outcome categories whereas, two stars were given to comparability. The scoring of overall study quality was done based on NOS evaluation of study quality.

2.5. Data synthesis

Narrative synthesis without *meta*-analysis was performed in this systematic review. This was because the included studies were heterogeneous with respect to PICO, and it was not possible to pool the results to estimate the combined effect. Furthermore, the variations in intervention made pooling together more challenging. The included studies only tended to describe a specific intervention resulting in majority of interventions being represented by a single study. Among six studies, two interventions had multiple studies but differed in type of drug, study population, route of administration and dosage. These studies were thus reported separately. To facilitate organization and analysis the selected studies were grouped together based on disease state (hypoglycaemia and DKA).

2.6. Certainty of evidence

The certainty of evidence was assessed according to the grading of recommendation, assessment, development, and evaluation (GRADE) approach. A web-based application, GRADE pro [20] was used to assess certainty of evidence of all included studies. Two reviewers (JM and SP) performed separate assessments of the certainty of evidence. In GRADE pro, the certainty of evidence based is assessed based on five domains-risk of bias, indirectness, imprecision, inconsistency, and likelihood of publication bias. Specific questions were presented in GRADE pro to address each domain and the reviewers provided responses selecting options such as serious, not serious, and non-suspected. After answering the questions, GRADE pro software produced a table with certainty of evidence as high, moderate, and low. Following the Murad et al [21] study to rate the certainty of evidence in absence of single pooled estimate, the certainty of evidence was obtained separately for cohort studies and randomized controlled studies.

3. Results

3.1. Study selection

The selection process and number of studies included/ excluded in each step are shown in Fig. 1 following the PRISMA reporting guidelines [15]. During the process, two studies could not be retrieved- one RCT registered in cinicaltrials.gov and one retrospective study published in 1994, which the university library could not retrieve, and the author did not respond to the article request. The list of excluded studies along with reason behind exclusion are elaborated in supplementary file 3. The reference list of systematic reviews and guidelines were reviewed for potential studies, but no new study was identified. During the screening process, if there was incomplete information or studies were not available for retrieval, the authors of publication were contacted via email, and two follow up emails were sent in the next 15 days. Among the four authors contacted, only two replied with the required information. Only studies with adequate information were included in the final review. Among six selected studies, five studies were focused on DKA, and one was on hypoglycaemia. Although, our eligibility criteria on study design were to include RCTs, cohort studies and case control studies, none of the studies with case-control design met our criteria. As a result, we ended up with only two RCT and four cohort studies.

3.2. Characteristics of included studies

Among six studies included in this study, the RCTs had a total of 143 participants and the cohort studies included 193,675 participants. Three of six studies were conducted in the United States of America (USA) while each of remaining studies were conducted in Australia, India, and Japan. Five out of six studies were focused on adults (age group of $\geq$ 16 years) whereas one study focused on children (12 years or younger). Table 2 and Table 3 display key characteristics of the included studies.

3.3. Quality assessment

Out of six included studies, the cluster randomized trial and parallel randomized trial showed low risk of bias and all cohort studies had high quality. The graph on quality illustrated in Fig. 2 was obtained from RoB2 tool and Table 4 (in supplementary file 2) was created manually to report quality of study from NOS.

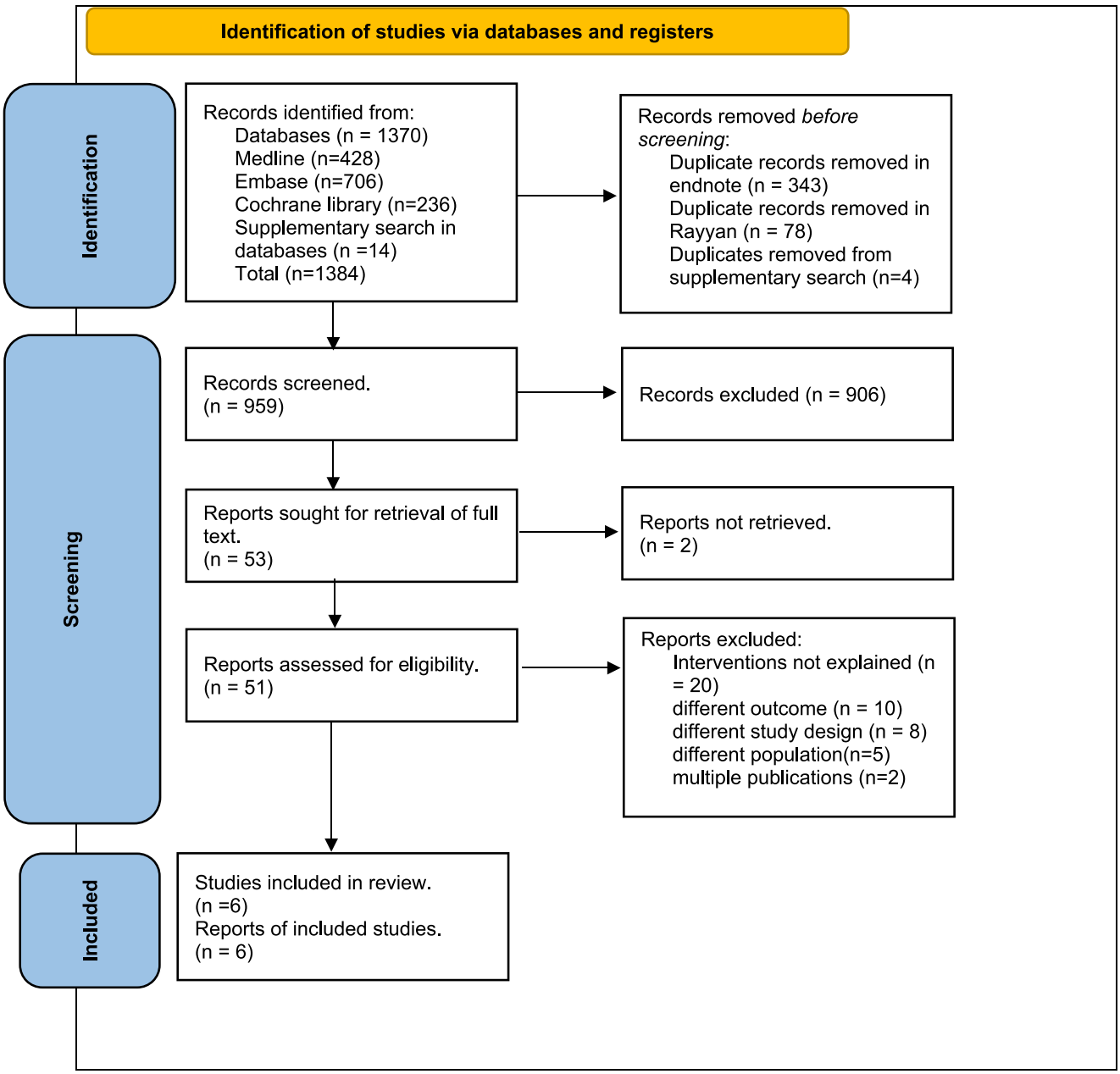

Fig. 1. Prisma Flow Diagram.

Table 2
Key characteristics of included experimental studies.

Author and year of publication	Setting	Target Condition	Study Design	Sample size	Population	Intervention	Comparator	Outcomes	Results
Mahesh Ramanan [22] 2021	Australia	Severe DKA	Cluster, crossover, randomized, controlled trial	93	All patients aged 16 or over presented with DKA	Plasmalyte-148 (PL)	0.9 % sodium chloride (SC)	Change in base excess, hospital mortality and lengths of stay	PL is noninferior to SC. ICU length of stay was 49 h (IQR 23–72) and 55 h (IQR 41–80) in the PL and SC group respectively
Karthi Nallasamy [23] 2014	India	DKA	A randomized clinical trial	50	Children 12 years or younger with DKA	Low dose insulin infusion (0.05 unit/kg/hour)	Standard dose insulin infusion (0.1 unit/kg/hour)	Rate of decrease in blood glucose, Time to resolution of acidosis, episodes of treatment failures	Low dose insulin is not inferior to standard dose insulin. time till resolution of DKA was 16.5 (7.2) hours in low dose group and 17.2 (7.7) hours, p value = 0.73 in standard group

Table 3
Key characteristics of included cohort studies.

Author and year of publication	Setting	Target Condition	Sample size	Population	Intervention	Outcomes	Results
Goad, N.T [24] 2019	USA	DKA	102	Adult patients 18 years or older with DKA	0.9 % Nacl and 0.45 % Nacl	In-hospital mortality, time to final DKA resolution	Hyperchloremia was associated with worst clinical outcomes such as higher APACHE II score (median 16, IQR (11.0–23.8)) longer in hospital length of stay and longer time to resolution of DKA.
Akira Okada 2021 [25]	Japan	DKA	14,216	Adult patients 20 years or older with DKA	Potassium therapy	In-hospital Mortality	Potassium replacement at < 10 mmol/L among patients with DKA was associated with higher mortality (n = 72).
Priya Rao [26] 2022	USA	DKA	5046	Adult patients with DKA	Subcutaneous insulin	Mortality, readmission, and length of stay	Use of subcutaneous insulin was associated with reduced ICU admissions and hospital readmissions (67.8 % to 27.9 %), with no change in length of stay and mortality
Kyle A. Weant [27] 2021	USA	Hypoglycaemia	311	Adult patients (≥18 years) treated for hypoglycaemia	10 % Dextrose (D10)	Efficacy of D10, Hospital mortality, length of stay	Average dose of 20gm of D10 and D50 are effective for treatment of prehospital hypoglycaemia, hospital mortality for D10 and D50 were 4.7 % and 6.2 % respectively.

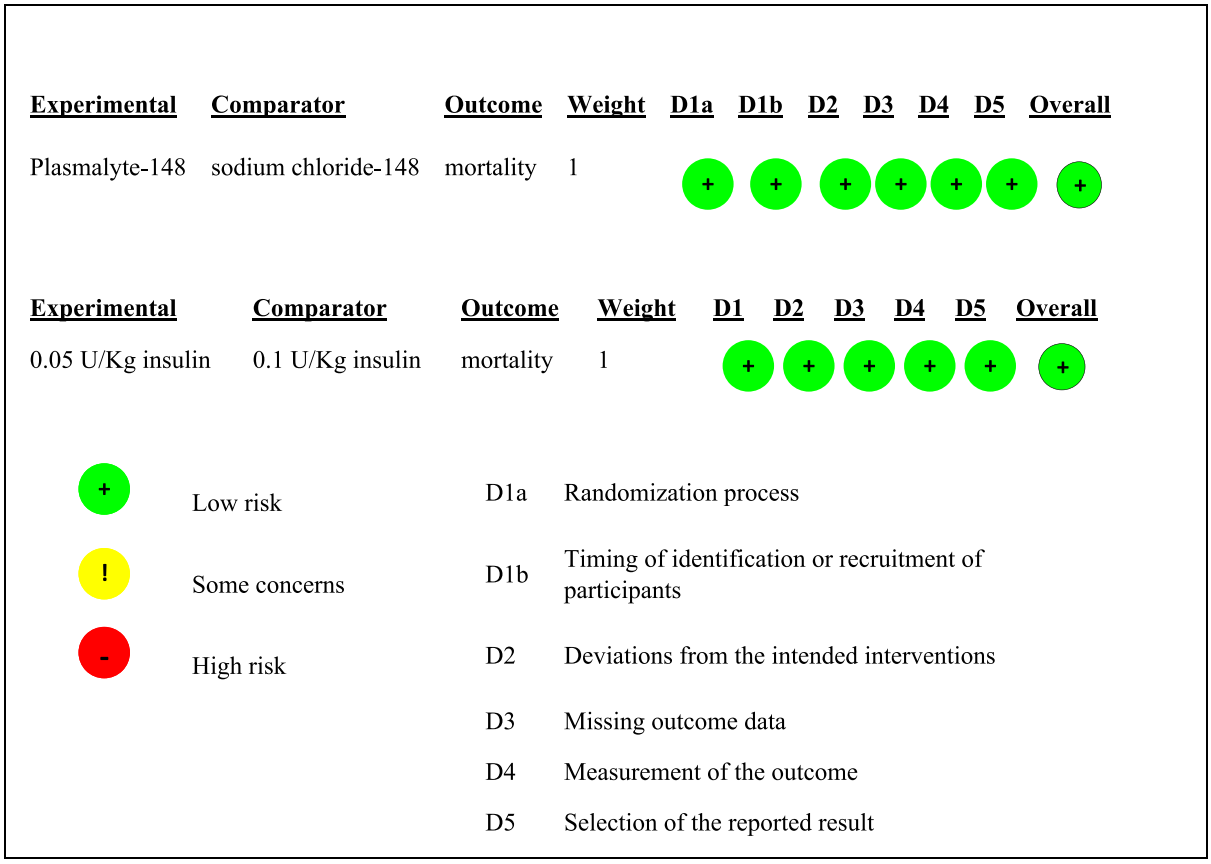

Fig. 2. Risk of bias in included RCT assessed by ROB2.

3.4. Result of individual studies

The selected six studies were heterogenous in characteristics, with each study focusing on a different intervention. The most common reported outcome was mortality and some of the studies reported outcomes like length of hospital stay and disease resolution. Although, the main outcomes of interest in this systematic review were mortality, DALYs and QALYs, the review also includes additional outcomes reported by the included studies. The interventions used in management of hypoglycaemia are oral glucose, oral carbohydrates, IV glucose, and IV dextrose. However, only the study on IV dextrose met our eligibility criteria. Similarly, management for DKA comprises of insulin, electrolyte therapy and IV fluids. Among these interventions, the eligible studies focused on insulin, potassium and IV fluids. The results of individuals studies are described below based on disease state (hypoglycaemia and DKA) and specific interventions reported in the included studies.

HYPOGLYCAEMIA

- **Dextrose**: A cohort study on 10 % dextrose (D10) [27], found both D10 and 50 % dextrose (D50) to be effective options for treatment of hypoglycaemia. In this study, no significant difference was found in

in-hospital mortality (4.7 % vs 6.2 %, p value = 0.623) or hospital admission rates (34.7 % vs 36.0 %; p value = 0.895, respectively). However, patients receiving D50 had significantly higher blood glucose level on arrival (129.5 vs 108.0 mg/dL; p value = 0.011) and had a significantly greater rise in blood glucose per gram of dextrose administration (6.4 vs 5.2 mg/dl; p value = < 0.05). This cohort study compared effectiveness of D10 with that of D50 in a pre-hospital setting.

DKA

- **Insulin:** A study evaluating subcutaneous (SQ) insulin with standard insulin infusion [26], found that SQ was effective in managing DKA. There were no significant changes in 30 days mortality before and post implementation (1 % vs 1.1 %), but there was a reduced rate of intensive care unit (ICU) admissions (adjusted rate ratio 0.43, 95 % CI, 0.33—0.56), and a decrease in proportion of hospitalization directly admitted to ICU rates from 67.8 % (202 hospitalizations) to 27.9 % (34 hospitalizations) with ($\chi^2 = 56.027$, p value < 0.001).
- A RCT conducted among children comparing insulin infusion at 0.05 unit/kg/hour vs 0.1 unit/kg/hour [23], showed low dose insulin was not inferior to standard dose insulin. There were no deaths reported in either group whereas, time till resolution of DKA was 16.5 (7.2) hours in low dose group and 17.2 (7.7) hours, in standard group (p value = 0.73) with similar rate of resolution of acidosis, serial changes in pH, bicarbonate and anion gap in both groups.
- **IV fluids**
  - Buffered salt solution: An open label cross-over cluster randomised trial [22] on Plasmalyte-148 (PL) (a buffered salt solution with lower chloride concentrations) found treatment with PL may result in faster resolution of metabolic acidosis. This study compared PL with sodium chloride (SC) and found 46 (96 %) patients in PL group and 36 patients (86 %) in the SC group attained base excess of ≥ -3 mEq/l at 48 h (h) post ICU admission. The odds of attaining base excess in PL group compared to SC group was 3.93 [95 % CI (0.73–2.16)], p value = 0.111. There was one death in the SC group and no death in PL group. The median ICU length of stay was 49 h (IQR 23–72) and 55 h (IQR 41–80) in the PL and SC group respectively. Similarly, hospital length of stay was shorter in PL group 81 h (IQR 58–137) versus 98 h (IQR 65–195) in the SC group.
  - Sodium chloride (0.9 and 0.45 %): A study examining the association of hyperchloremia on hospital outcomes in DKA [24] found the development of hyperchloremia being associated with worse clinical outcomes such as low APACHE II score (median 16, IQR (11.0–23.8)) and development of comorbidities. Although, there was no mortality in either of the groups, the median volume of fluid resuscitation was significantly higher in hyperchloremia cohort 5819 (IQR: 4098–8138) ml vs 3915 (IQR: 2939–5230) ml with p value = <0.001 in normochloremia. Similarly, patients had significantly longer median DKA resolution time 22.3 [IQR: 15.2–36.9] in hyperchloremia vs 14.2 [IQR: 8.8–21.1] hours in normochloremia; p value = 0.001. Median length of hospital stay was significantly longer in hyperchloremia 97.1 [IQR: 68.8–138.2] vs 58.7 [IQR: 43.3—88.2] in normochloremia, p value = 0.001. In this study patients were treated with 0.9 % NaCl or 0.45 % NaCl and the patients were divided into 2 cohorts based on serum chloride levels, hyperchloremia was defined as a serum chloride ≥ 109 mEq/L and normochloremia was defined as a serum chloride ≤ 109 mEq/L.
- **Electrolytes**
  - **Potassium:** A study that evaluated potassium infusion [25], found patients treated with potassium at concentrations of 10 to 40 mmol/l had similar in-hospital mortality rates whereas, patients treated with lower potassium concentrations (<10 mmol/l) had higher mortality with odds ratio [OR]: 2.49[95 % CI (1.55 to 1.06)], p value < 0.001. The number of deaths were higher in low concentration group (n = 72), p value < 0.001 compared to 39, 27 and 27 in medium–low, medium–high, and high concentration groups respectively. In this study, patients were divided into groups according to potassium concentrations, the groups were low =≤7.6 mmol/l, medium–low = 7.7 – 11.4 mmol/l, medium–high = 11.5 – 16.0 mmol/l and high = ≥16.1 mmol/l.

3.5. Certainty of evidence

The cohort studies had low certainty of evidence whereas, the RCTs had high certainty of evidence. The reason behind the low scoring of cohort studies was due to their nature as an observational study, which inherently starts with a low confidence. The Table 5 (Supplementary table 2) illustrates certainty of evidence of this systematic review, the rating was done with reference to Murad et al [21].

4. Discussion

4.1. Summary of main findings

Based on results from the included studies, this systematic review suggests that both 50 % dextrose and 10 % dextrose are effective treatments of hypoglycaemia in a pre-hospital setting. Likewise, for resolution of DKA IV insulin and SQ insulin, fluid therapy by PL and SC had better effect with shorter length of hospital stays. Similarly, potassium concentration of less than 10 mmol/l increases mortality and overuse of fluids with chloride is associated with increased hospital length of stay and risk of developing comorbidities. The results are based on a single study and hence, more systematic reviews are required in future.

4.2. Overall completeness and applicability

In this systematic review, we searched for literatures focused on effectiveness of interventions on management of acute complications (hypoglycaemia and DKA) of DM without any limits on publication dates. We however included limitations on study design (only RCT, cohort and case-control studies) and language. Out of the 53 studies reviewed for eligibility only six were included in the review. All the studies included are of good quality and the evidence base to support the RCTs is quite strong. We faced some challenges during the review, as we decided to restrict the study design, resulting in exclusion of some case reviews and medical record reviews. Also, studies on interventions not included in WHO-UHC compendium such as glucagon were excluded from the review. Only one study on hypoglycaemia met the eligibility criteria, so, the effectiveness of interventions apart from IV dextrose could not be fully assessed in this study. This systematic review also identified that there is limited literature from LMICs and LICs on this topic. During this systematic review, we observed that there is an evidence gap for both hypoglycaemia and DKA management. The number of studies on DKA was higher compared to those on hypoglycaemia which might be due to severity of DKA requiring medical assistance. We argue that more studies on effectiveness of interventions should be carried out, particularly in LMICs and LICs based on their local guidelines and management policies. Conducting more RCTs and high-quality observational studies on the effectiveness of the interventions listed in WHO-UHC compendium with larger sample sizes across different settings would strengthen the evidence base on effectiveness of interventions for emergency care in DM.

4.3. Implications for practice

Based on this systematic review, we suggest using both 10 % and 50 % dextrose for hypoglycaemia. Having alternatives will be beneficial especially for low-income settings as people in these setting is often not treated due to lack of resources [13,14]. For management of DKA, timely management by fluid restoration and insulin administration is very crucial. we were unable to strongly suggest the type of fluid due to lack of enough studies. Similarly, potassium concentrations must be between 10 and 40 mmol/l to prevent mortality among DKA patients.

The results from this systematic review should be adapted by policy makers with caution. The included studies were mostly conducted in HICs which may present practical challenges while adapting these interventions to low-income settings.

4.4. Comparison with other studies and guidelines

Among the interventions suggested by guidelines from WHO, ADA, JBDS-IP, and other similar guidelines, we found studies on dextrose, insulin, IV fluids and potassium based on eligibility criteria. For management of hypoglycaemia WHO [28] guidelines recommends use of carbohydrate and IV dextrose whereas, ADA [8] recommends use of any form of carbohydrate and glucagon. We did not include studies on glucagon because we focused on looking at effectiveness of interventions listed by WHO-UHC compendium. We found two systematic reviews on DKA [29,30] targeted to specific interventions such as insulin and intravenous fluids with different outcomes than our systematic review. We also found evidence review [31] but this review was not based on experimental studies or high-quality observational studies and had different outcomes than out systematic review. We ended up with few studies compared to other studies [29–31] because we were evaluating effectiveness based on mortality, DALYs and QALYs as our main outcomes and we only included studies with randomized control design, cohort design and case-control design. Despite of the guidelines formulated by WHO [28] and ADA for management of hypoglycaemia and DKA, it is not widely followed by many countries and most of the hospitals either follow the local protocol or no protocol [12,13]. The treatment guideline used may or may not have interventions that are shown to be effective. For example some of the HICs use glucagon for managing hypoglycaemia at home or in the hospital [32,33] which has proven to be very effective [34,35]. However, this intervention is not included in the WHO UHC compendium list.

A study on hypoglycaemia has highlighted underreporting issues for both patients (due to hesitations) and providers (lack of interest due to minor issue) [2]. Despite the high economic burden associated with the management of hypoglycaemia, there is a lack of enough data on management of hypoglycaemia and related outcomes [31,32]. This shows the need to conduct studies on hypoglycaemia outside the hospital settings.

While researchers attempt to strengthen evidence base for effectiveness of interventions for the management of diabetic emergencies, it would also be important to include cost effectiveness component. A cost effectiveness analysis of interventions to prevent and manage diabetes [36] have suggested most cost saving and very cost-effective interventions; the interventions for management of acute complications are however lacking. Furthermore, conducting cost-effectiveness analysis of these interventions will be important to inform policy makers in their decision-making process to choose the most appropriate and cost-effective intervention.

4.5. Strength and limitations

There are several strengths of this systematic review. Primarily, the review protocol was registered in PROSPERO database and followed PRISMA guidelines. A comprehensive search strategy was used to identify studies. We have highlighted the knowledge gap in available literature. We have maintained overall quality of study as two independent reviewers were responsible for study selection, data collection, data extraction and assessment quality of study of included studies. Although this systematic review tried to summarize all the available evidence on interventions there are some limitations to be acknowledged. This review only included people with type 1 and type 2 DM and did not include other types of diabetes such as gestational diabetes mellitus and diabetes insipidus. The results from this systematic review cannot be generalized to all age groups. Additionally, this review excluded study designs like cross sectional studies or case reports or medical record review hence, we could not provide strong evidence base for all the interventions. While the included studies were of high quality, it should be noted that the certainty of evidence of cohort studies was low. Considering the limited number of studies particularly RCTs, and majority of the studies from HICs, the evidence from this systematic review needs to be applied with caution considering local context.

5. Conclusion

We conclude the interventions for management of diabetic emergencies to be effective for the outcomes assessed in this systematic review. Either of the 10 % or 50 % dextrose is effective for the management of hypoglycaemia against mortality and length of hospital stay. In case of DKA subcutaneous insulin over IV insulin therapy, potassium between 10 and 40 mmol/l, chloride levels in normal range ($\leq$109 mEq/L), IV fluids like Plasmalyte and normal saline are effective against mortality, length of hospital stay, ICU admission and disease resolution.

This evidence could be helpful to guide development of guidelines for management of diabetic emergencies such as DKA and hypoglycaemia in both HICs and LICs with careful consideration of local contexts. Considering the dearth of primary studies, more RCTs and high-quality analytical studies with larger sample size targeting the interventions listed in WHO-UHC compendium as well as newly developed interventions might help strengthen the evidence base. More studies could be considered on hypoglycaemia both in the hospital setting and outside. Inclusion of cost effectiveness analysis of effective interventions would allow a better decision support for policy makers and program managers.

CRediT authorship contribution statement

Jasmine Maharjan: Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. **Sagar Pandit:** Methodology. **Kjell Arne Johansson:** Supervision, Writing – review & editing. **Pratik Khanal:** Supervision, Writing – review & editing. **Biraj Karmacharya:** Supervision, Writing – review & editing. **Gunjeet Kaur:** Supervision. **Krishna Kumar Aryal:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.111078.

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