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Tittel: Does timing of intra-articular glucocorticoid injections impact infection rates in subsequent arthroplasty?

A systematic review of the literature

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Contents

Abstract

Purpose: Intra-articular injections are widely used to treat different joint pathologies. In the literature, there is conflicting evidence on the infection rate after use of intra-articular glucocorticoids to subsequent arthroplasty. The purpose of this systematic review was to investigate the infection rate of intra-articular corticosteroid injections performed with different time intervals preoperative on subsequent arthroplasty and to compare it with a control group.

Design: Systematic review of cohort studies.

Methods: A systematic search for reports of cohorts was performed by a single reviewer on the 24.04.2022 in the electronic databases PubMed and Embase. Comparative studies with controll and injection group, using glucocorticoid injection intra-articulartly with spesific time intervalls prior to arthroplasty were included. There were no language restriction. The search terms were 'total knee arthroplasty', 'replacement', 'corticosteroid', 'steroid', 'infection', 'safety'. Risk of bias was assessed by a single reviewer using the Newcastle-Ottawa Scale.

Results: 7 cohorts (n = 7) were included in a narrative analysis. Time span between intra-articular corticosteroid injection and surgery was divided into two-month intervals preoperatively, respectively 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 months. Based on the Newcastle-Ottawa Quality Assessment Scale, included studies score between 7-9 which give them high methodology quality and low risk of bias. There was an 1% increase in infection rate among the participants in the injection group compared to the controll group prior to arthroplasty. The percentage was similar throughout the different time intervals. Number needed to harm was estimated to be 198 (95 % CI [149, 248]).

Conclusion: The results indicate that the use of intra-articular gluccorticoids increase the risk of post-operative infection.

Sammendrag

Formål: Intraartikulære injeksjoner er mye brukt til å behandle forskjellige leddpatologier. I litteraturen er det motstridende forskningsbelegg knyttet til infeksjonsraten etter bruk av intraartikulære glukokortikoider i forkant av leddoperasjon. Hensikten med denne systematiske oversikten er å undersøke infeksjonsraten knyttet til utførelse av intraartikulære kortikosteroidinjeksjoner utført med forskjellige tidsintervaller preoperativt sammenlignet med kontrollgruppe som ikke mottar kortikosteroidinjeksjoner preoperativt.

Design: Systematisk oversiktsartikkel av kohortstudier

Metoder: Et systematisk søk av kohortstudier ble utført av en medarbeider den 24.04.2022 i de elektroniske databasene PubMed og Embase. Studier med komparative design med kontroll- og injeksjonsgruppe, der glukokortikoidinjeksjoner intraartikulært er utført med spesifikke tidsintervaller før leddoperasjon ble inkludert. Det var ingen språkbegrensninger i inkluderte artikler. Søkebegrepene var total knee arthroplasty', 'replacement', 'corticosteroid', 'steroid', 'infection', 'safety'. Risiko for systematiske skjevheter i inkluderte studier ble vurdert av en medarbeider ved bruk av Newcastle-Ottawa-skalaen.

Resultater: 7 kohorter (n = 7) ble inkludert i en narrativ analyse. Tidsrom mellom intraartikulær kortikosteroidinjeksjon og operasjon ble delt inn i to-måneders intervaller preoperativt, henholdsvis 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 måneder. Basert på Newcastle-Ottawa Quality Assessment Skalaen, inkluderte studier skårer mellom 7-9 som gir dem høy metodekvalitet og lav risiko for skjevheter. Det var en økning på 1 % i infeksjonsraten blant deltakerne i injeksjonsgruppen sammenlignet med kontrollgruppen som ikke fikk kortisoninjeksjon preoperativt. Prosentandelen var lik gjennom de forskjellige tidsintervallene. Antall som må behandles ble estimert til å være 198 (95 % KI [149, 248]).

Konklusjon: Resultatene indikerer at bruk av intraartikulære glukokortikoidinjeksjoner preoperativt øker risikoen for postoperativ infeksjon.

Introduction

Background

The general intention in musculoskeletal pathologies is in most cases from conservative, to minimally invasive to operative procedures. A large number of pathologies that physiotherapists treat regards joint pathologies. Intra-articular injections are widely used as a primary treatment, as a treatment to delay surgery or as a diagnostic tool to distinguish between pain from a specific joint and referred pain.

In Norway there is no consensus regarding a waiting time after intra-articular corticosteroid injection prior to joint arthroplasty. There is though a clinical practice of 3 months regarding knee and hip arthroplasty. Nevertheless, there is discrepancy of waiting time regarding other type of surgeries of the same joints, such as diagnostic or operative arthroscopies, as well as other joints surgeries than hip and knee.

There have been clinical concerns that the chronological proximity of an injection to subsequent arthroscopy may predispose to infection in the injected joint (Byrd et al., 2019a; Cancienne et al., 2015a; Charalambous et al., 2014). In the literature, there is conflicting evidence regarding the topic as shown from different systematic reviews. There is also conflicting evidence on the time aspect of the injection performed with different time intervals prior to joint arthroplasty, with studies showing low risk of infection when injection is performed at >3 months, while other studies showing higher risk of injection is also shown from periods between 3-11 months. It has previously been proposed that the residual effects of the steroid injection subside at approximately 11 months.

Reported side effects following the use of intra-articular glucocorticoids for subsequent arthroplasty are deep infections, superficial infections and joint sepsis. This process requires best evidence based clinical judgement, which means that clinical physiotherapists considers the professional rules, knowledge and practices in relation to the patient´s needs, wishes and life situation and in collaboration with the physician.

As the evidence is conflicting, I would like to investigate the current literature for evidence regarding this topic.

Theoretical context

Intra-articular steroid injections are widely used to treat pain and inflammation in joint pathologies (Marsland et al., 2014). Such intervention is also used as treatment where physical therapy did not result in desired effect, where NSAIDS/pharmacological intervention had a weak or no effect or as an attempt to minimize systemic effet (Marsland et al., 2014). Furthermore injection therapy has been used as a mediator to postpone surgery, for patients not willing to receive surgery or when there is contraindication to undergo surgery at a particular period (Li et al., 2018). Addditionally they may be used as a differential diagnostic tool in order to distiguish between pain originating from intrinsic factors from extrinsic sources of pain; distinguishing arthritis joint pain of the glenohumeral joint from discoradicular cervical pain radiating distal to the deltoid region (Li et al., 2018).

There are cases where the desired effect from one or more intra-articular injections is not achived at all, the effect is short term or with recurrence within weeks or months post injection (Kokubun et al., 2017). As the intention to treat is in many cases from conservative, to minimal invasive to operative prosedures, such patients not effectively controlled with the first two mentioned procedures, may be in need of an operative intervention (Li et al., 2018; Marsland et al., 2014). Data shows that 20-30% of TKA will have received intra-articular steroid injections prior to surgery (Marsland et al., 2014; Turcotte et al., 2020).

Reported adverse effect after use of intra-articular use of glucocorticoids to subsequent arthroplasty are deep infections, superficial infections and joint sepsis.

There have been clinical concerns that the chronological proximity of an injection to subsequent arthroscopy may predispose to infection in the injected joint (Byrd et al., 2019a; Cancienne et al., 2015a; Charalambous et al., 2014; Sascha Colen et al., 2021; Kokubun et al., 2017; Li et al., 2018; Marsland et al., 2014; Pereira et al., 2016). The rate of infection has been shown to increase with 50% if performed within the 3 month range (Schairer et al., 2016b).

It has been suggested that the reason of increased infection rate may be due to due to failure of the steroid to dissolve and thus cause local immunosupression following joint arthroplasty (Kaspar & De, 2005a; Papavasiliou et al., 2006). It has also been proposed that contamination may arrise as a consequense of lack of sterility precautions that are applied during the injection process that often vary among clinicians (Charalambous et al., 2003).

Previous research done on this particular topic include primarity cohort studies; retrospective and prospective. Cohort studies is one of the two main types of observational studies (Song & Chung, 2010) and is the main type of observational study conducted to investigate intra-articular injections prior to joint arthroplasty, as randomized controlled trials are not indicated and are unethical to conduct (Song & Chung, 2010). Systematic reviews summarising and comparing the results have been contradictive and inconclusive on the timeframe of intra-articular injections prior to joint arthroplasty.

In a 2014 study, Marsland and colleagues included 4 studies in their research investigating intra-articular injection in the knee joint prior to arthroplasty (Marsland et al., 2014). The studies included were 2 retrospective case controll and 2 cohort being level three evidence due to the fact that no level one or two studies were available for review. The author concluded that of the four studies included only one showed incresed risk of infection rates. Of the three remaining the author described the studies as underpowered and with risk of selection bias.

In an other systematic review from 2014 (Charalambous et al., 2014), 8 studies were included regarding both hip and knee joint. Single case reports, reviews, and non-comparable studies were excluded. The author concluded that no significant effect of infection rate was found to intra-articular joint injection to consequent arthroplasty.

In 2016 Pereira and collegues included 9 studies that focus only on hip injections prior to arhtroplasty, no prospective studies were included (Pereira et al., 2016). The included retrospective studies included were described with lack of information about methodology as a consistent flaw. The author concluded that there is insufficient evidence to conclude that it increases infection rate.

Last, but not least, Li and colleagues reviewed in 2018 all systematic reviews currently done to select best evicence and consider all risk of bias in the included litterature in order to provide recommentations through best evidence (Li et al., 2018). 6 systematic reviews were included, AMSTAR instrument and ROBIS tool were used to quilify the included articles respectively. Heterogeneity information within each variable was extracted from the included studies. The Jadad algorithm was then used to determine which systematic reviews can provide the best evidence. The author concluded that there was no significant effekt and considered the evidence as weak regarding the waiting time frame for intra-articular injections prior to arthroplasty.

Even recent studies performed in 2021 have been contradictive to each other. One study investigated intra-articular corticosteroid injection into the thumb carpometacarpal (CMC) joint for the treatment of arthritis within the 3 months before CMC joint arthroplasty or arthrodesis. There were 3 groups: (1) no thumb injection within 6 months of CMC joint surgery, (2) thumb injection between 3 and 6 months before CMC joint surgery, and (3) thumb injection within 3 months before CMC joint surgery, showing that intra-articular injection of glucocorticoid 3months prior to arthroplasty increased the risk of infection (Qin et al., 2021).

Kurtz in his study evaluated whether the preoperative use and timing of the use of hyaluronic acid (HA) and/or corticosteroid (CS) injections were associated with an increased risk of periprosthetic joint infections (PJIs) following primary total knee arthroplasty (TKA). Association between PJI risk and (1) injection type; (2) timing; (3) patient demographic factors; and (4) surgery-related factors, such as surgeon injection volume, knee arthroscopy (pre- and postoperative), and hospital length of stay were measured and the author found that there was no risk of increased infection when injection is administered within 3 months prior to surgery (Kurtz et al., 2021).

Neither Grondin and colleagues found an increased rate of infection when intra-articular injection was administered within 3 months of knee arthroplasty. In his prospective cohort study 304 patients were recruited with mean follow-up time 24.9 months and the author did not find an increased prevalence of infection among the participants of the injection group that received injection with 3 months to arthroplasty (Grondin et al., 2021).

In a 2021 study Forlenza concluded that it appears to be both a time and dose-dependent association of hip corticosteroid injection (CSI) and periprosthetic joint infection (PJI) following total hip arthroplasty. CSI within 4 months of surgery was associated with a higher incidence of PJI at 6-month follow up. In addition the author concluded that an injection within 1 month of surgery corresponded to a higher odds of PJI than an injection 4 months prior to surgery (Forlenza et al., 2021b). Similar results were seen by Colen and colleagues were IAHA performed 6 months or less prior to THA may pose a risk for increased rates of PJI. The author recommends refraining from performing THA within 6 months after IAHA administration (S. Colen et al., 2021).

Conclusively**,** as mentioned by several authors, there is a dichotomy on the topic, both in terms of infection rate but also on the waiting time interval prior to joint arthroplasty.

Purpose statement

There are contradictive results between previously published reviews and between recent studies. There is also conflicting evidence on the time interval of injection prior to surgery varying from 3 to 6 months, in addition to data suggesting a waiting time up to 11 months when the residual effects of the steroid injection are supposed to have subsided.

It is of essence that such a topic is enlightened from a patient perspective taking into account the high rate of arthroscopies, arthroplasties and general joint surgeries in the increasing life expectancy of the population. The patient should receive best possible evidence based treatment regardless of country, city or surgeon.

Hypothesis

Does timing of intra-articular glucocorticoid injections affect infection rates in subsequent arthroplasty/surgery?

Methods

Research design

To investigate this hypothesis, I have chosen to perform a systematic analysis of cohort studies. This is widely used for this type of hypothesis (Charalambous et al., 2014; Li et al., 2018; Marsland et al., 2014; Pereira et al., 2016) and has previously been applied by other systematic reviews.

Cohort studies is one of the two main types of observational studies (Song & Chung, 2010). To address some investigative questions in plastic surgery, randomized controlled trials are not always indicated or ethical to conduct (Song & Chung, 2010). Another example of studies being unethical to perform an RCT would be the effect of smoking on lung carcinoma. Thus, observational studies being the most suitable research method to address such questions.

Well-designed observational studies have been shown to provide results similar to randomized controlled trials (Song & Chung, 2010). Cohort studies offer specific advantages by measuring disease occurrence and its association with an exposure by offering a temporal dimension (Song & Chung, 2010).

In the case of intra-articular injection, it would be unethical to expose participants for injection procedure prior to arthroplasty and risk side effects reported in the literature. Therefore, the systematic analysis includes cohort studies done prospectively and retrospectively investigating the infection rate of intra-articular injection as an aspect of chronological proximity to arthroplasty.

Inclusion and Exclusion

Generalizability is a term used in academic settings by researchers and is of essence when conducting research. It can be defined as the extension of research findings and conclusions from a study conducted on a sample population to the population at large (Jeffrey Barnes, 1994-2021). Thus, it is important to establish inclusion and exclusion criteria in order for the reader to know which group the research can be applied to (Carter & Lubinsky, 2016).

The inclusion and exclusion criteria for this particular systematic review are:

- Only studies that have used intra-articular glucocorticoids injections prior to surgery are included.

- Only comparative studies that have both controll and injection-group are included

- Time-point of injection prior to surgery. Only studies with time spesific measurements for the intra-articular injection prior to surgery are included.

- Prospective controlled cohort studies

- Studies reported in any language are identified

Variables

In this systematic review all type of infections are considered in the analysis. This type of analysis can give an overall impression of infection/no infection as different types of infection have been measured among different studies included.

Risk ratios of infection and 95% confidence intervals should be mentioned in the papers included.

Injection technique should be mentioned clearly in the included articles.

Time between the steroid injection and arthroplasty should be mentioned.

Data collection

A systematic literature review of cohort studies related to the timing of intra-articular steroid injection prior to arthroplasty and the subsequent risk of infection was performed in two databases; PubMed and EMBASE. Data is collected and analysed by a single reviewer.

The search was conducted for studies published until 15.04.2022 using a combination of keywords as shown below:

1. Intra-articular: "intra-articular" AND injection*
2. Safety: safety, infection*, risk, sepsis
3. Surgery: surgery, surgeries, arthroplasty, arthrodesis, postoperative, "post-operative", preoperative, "pre-operative"
4. Steroids: corticosteroids, steroids

MeSH terms will be combined to get a broader and better combination of words.

1. Intra-articular: injections, intra articular
2. Safety: Postoperative Complications, infections
3. Surgery: surgical procedures, operative
4. Steroids: glucocorticoids

Inclusion and exclusion criteria should be met by the included articles as well as the variables that need to be described by the articles in order to include an article. All research papers not satisfying the above mentioned criteria will be excluded.

The process will be shown in stages for visualisation and reproducibility for future research.

The purpose of this paper is to base the research method as close as possible to the recommendations of the later review articles on the topic where suggestions for improvement are listed.

In total there were 714 articles after completing the search process in both PubMed and Embase. In addition, I extracted 3 articles from articles making the total number of articles to 717 articles. All articles were imported in EndNote.

Through EndNote I performed duplication removal deleting 193 articles being duplicates. All duplicates were checked one by one before removing and were finally moved in a separate folder within EndNote. That leaves 526 articles after this particular step.

All the 526 articles were thoroughly checked and 501 articles were irrelevant in terms of topic. Of the remaining 25 articles 2 conference abstracts and 16 journal articles were excluded (n=18) for either lacking necessary data for analysis or not meeting one or more of the inclusion criteria:

Two abstracts from Hip International conference and one journal article were excluded for not providing sufficient information to interpret, intervals for when the injections were performed was not mentioned and due to lack of time no intent of contact was established with the authors to retrieve information (Desai et al., 2009; Glover & Gunasekaran, 2014; Meermans et al., 2010).

Tow articles registered injections performed through questionnarie and all types of injections were allowed for the particupants to register in both those articles (Horne et al., 2008; Turcotte et al., 2020). As only intra-articular, in particular glucocortoid injections, are included in this meta-analysis both those articles are exluded due to that.

One article was excluded as being a pilot study with few participants (Papavasiliou et al., 2006).

One article was exluded for injecting local anestheticum in combination with glucocorticoids and in addiction there is no available data regarding time intervall of injection pre-operatively (Chitre et al., 2007).

Two articles were excluded as the injection was performed intra-operatively (Cancienne et al., 2016; Kohls et al., 2022).

Two articles were excluded for not mentioning time intervall of injection prior to joint arthroplasty (McIntosh et al., 2006; McMahon & Lovell, 2012)

One article was excluded for comparing corticosteroids or hyaluron acid prior to total knee arthroplasty, and in addtion only examining a 3 months time intervall and no other time intervalls (Richardson et al., 2019).

Four studies were excluded for not having a controll group (Byrd et al., 2019b; Kokubun et al., 2017; Sankar et al., 2012; Sreekumar et al., 2007).

Two studies were excluded as they we examining the affect of one versus several injections prior to joint arthroplasty (Chambers et al., 2017; Forlenza et al., 2021a)

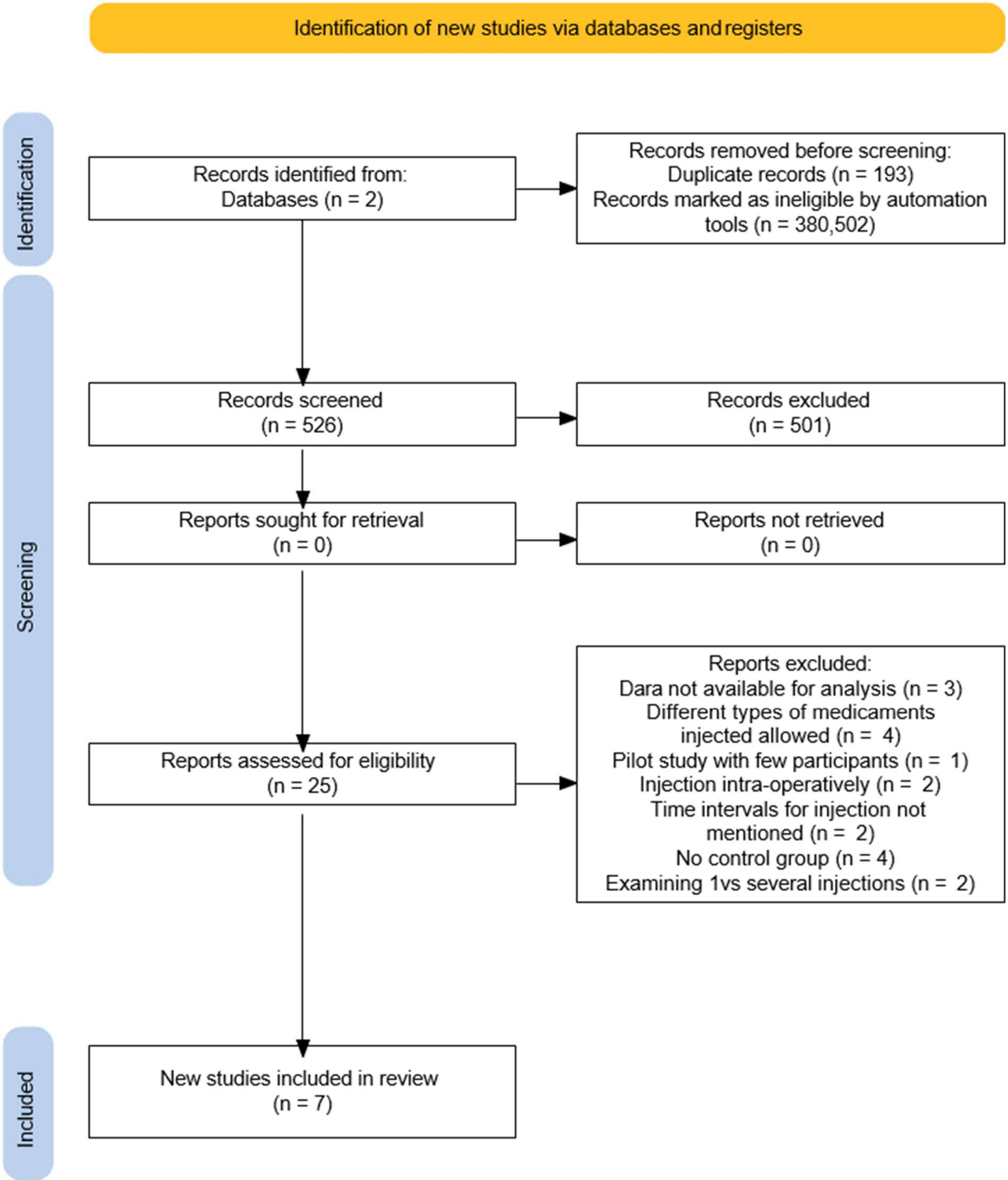

Figure 1: Prisma 2020 flow chart (Page et al., 2020)

There are seven articles in total that satisfy the inclusion criteria that will be included in the systematic review. Characteristics of the studies are illustrated in table 1. Study type and joint type arthroplasty has been mentioned for all included studies. The type of steroid injection of all studies possible to retract the information has been mentioned as well as the number of participants in both injection and control cohort groups has been numbered.

Time to surgery has been mentioned as a total time from the first time interval to the last time interval each study measured, even though all studies have investigated different time intervals for injection prior to surgery, which will be mentioned during the results and data analysis. Lastly, the findings of each study are summarized.

Tabell 1: Included studies Investigating the Effect of the Timing of Preoperative Corticosteroid Injections on postoperative infection rate.

AUTHOR ET AL	STUDY TYPE	PARTICIPANTS INJECTION/CONTROLL	JOINT	STEROID INJECTION	PRECAUTIONS	TIME TO SURGERY	FOLLOW UP	FINDINGS
LEE 2022	Retrospective	290/72089	Knee	Triamcinolon >80mg	Aseptic technique	0-6 months	1 year	Increased risk of infection with 2 weeks interval
CANCIENNE 2019	Retrospective	2724/4670	Knee	Triamcinolon/ methylprednisolone >80mg	Aseptic technique	2-8 weeks	3 months	Increased risk of infection with 3 months interval
BHATTACHARJEE 2021	Retrospective	8226/68744	Knee	Not Applicable	Aseptic technique	0-6 months	1 year	Increased risk of infection with 4 weeks interval
MEERMANS 2012	Retrospective	175/175	Hip	Methyl prednisolone 80mg	Aseptic technique	0-12 months	1 year	No infection rate was found
SCHAIRER 2016	Retrospective	5421/168537	Hip	Not Applicable	Aseptic technique	0-12 months	1 year	Increased risk of infection with 3 months interval
AMIN 2016	Retrospective	360/845	Knee	Not Applicable	Aseptic technique	0-12 months	7 years	No infection rate was found
CANCIENNE 2015	Retrospective	22240/13650	Knee	Not Applicable	Aseptic technique	0-9 months	1 year	Increased risk of infection with 3 months interval

Risk of Bias analysis

The methodological quality and risk of bias of included systematic reviews were assessed by the Newcastle-Ottawa Quality Assessment Scale (NOQAS) for cohort studies instrument. The NOQAS is a tool used for assessing the quality of non-randomized studies included in a systematic review and/or meta-analyses. Using the tool, each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars.

The method was developed as a collaboration using a Delphi process to define variables for data extraction. The tool was then tested on systematic reviews and further refined (Deeks, 2003). Separate tools were developed for cohort and case–control studies. It has also been adapted for prevalence studies (Mata et al., 2015; Rotenstein et al., 2016; Rotenstein et al., 2018). Based on the NOQAS, included studies score between 7-9 which give them high methodology quality and low risk of bias. One study score 7/9, four score 8/9 and two score 9/9.

Table 2: Critical Appraisal using Newcastle-Ottawa quality Assessment scale for cohort studies

Criteria	Lee et al	Bhattacharjee et al	Cancienne et al	Meermans et al	Schairer et al	Amin et al	Cancienne et al
Representativeness of the Exposed Cohort	1	1	1	1	1	1	1
Selection of the Non-Exposed Cohort	1	1	1	1	1	1	1
Ascertainment of Exposure	1	1	1	1	1	1	1
Demonstration That Outcome of Interest Was Not Present at Start of Study	1	1	2	1	1	1	1
Comparability of Cohorts on the Basis of the Design or Analysis	1	2	1	1	1	1	2
Assessment of Outcome	1	1	2	1	1	1	1
Was Follow-Up Long Enough for Outcomes to Occur	0	1	0	1	1	1	1
Adequacy of Follow Up of Cohorts	1	1	1	1	1	1	1
TOTAL	7	9	8	8	8	8	9

Results

In total, 373.106 patients who underwent joint arthroplasty were included in this study. These patients were divided into two different cohort groups: The injection cohort included 46.910 patients (7.95%) who received intra-articular corticosteroid injections prior to joint arthroplasty during different time intervals; the control cohort included 326.196 patients who did not have any history of intra-articular corticosteroid injection prior to joint arthroplasty.

Infection rate is described with odds ratio with 95% confidence intervals (CI) for the respective time intervals described below.

Type of infection varies in terms of description, but in general terms all researchers have distinguished between deep/narrow type requiring surgical debridement or more invasive type of follow up and superficial/broad type of infection requiring medical intervention; In this systematic review all type of infections are considered in the analysis. This type of analysis can give an overall impression of infection/no infection as different types of infection have been measured among different studies as seen in table 3.

Time span between intra-articular corticosteroid injection and surgery was divided into two-month intervals preoperatively, respectively 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 months. Firstly, was it an attempt to see if the infection rate changes in the preoperatively time between 0 to 3 months which most studies have examined. In addition, a two-month interval had a higher rate of overlap between the studies making it able to make better overlap over the participants between the different studies included.

The data from the different studies is first summarized in the table below. Here, we consider different time - windows for the time from injection to surgery, where a patient is considered to have received an injection in a given window if this has any overlap with the window in the original study.

Tabell 3: All included studies with an overview over type of infection and its definition.

AUTHOR ET AL	TYPE OF INFECTION	DEFINITION OF INFECTION
LEE 2022	Broad and narrow	A broad definition of infection using knee infection diagnoses and a narrow definition of infection requiring surgical debridement.
CANCIENNE 2019	All types of infections considered in the analysis	10180 Incision and drainage of complex wound infection 20005 Incision and drainage of soft tissue abscess, subfascial 27310 Arthrotomy, knee, with exploration, drainage, or removal of foreign body, infection 29871 Arthroscopy, knee, surgical; for infection, lavage, and drainage
BHATTACHARJEE 2021	**Narrow definition**	The diagnosis of postoperative TKA infection was defined by patients who underwent revision surgery secondary to surgical site infection within 1-year after surgery.
MEERMANS 2012	Deep Periprosthetic Joint and superficial	**Deep PJI**: PJI was defined as (1) a sinus tract communicating with the implant, (2) the identical pathogen isolated from two or more separate tissue samples, or (3) the presence of purulence in the joint. Growth from one specimen only usually was regarded as a contaminant, but only after discussion with a consultant microbiologist who specialized in bone and joint infection and after reviewing all available data from that patient **Superficial** 29]. A superficial infection was defined as any wound infection that involved only the skin and subcutaneous tissue that was confirmed with ultrasound or during surgical debridement, an organism isolated from an aseptically obtained culture, or signs of infection including a painful wound, swelling, redness, or heat [All patients received antibiotics pre and post surgery
SCHAIRER 2016	Periprosthetic infection	postoperative periprosthetic infection within 1 year of THA, determined by hospital readmission with a procedure for infection: irrigation and debridement, implant removal with placement of cement spacer, or revision hip arthroplasty with a concurrent diagnosis of infection
AMIN 2016	**Deep infection**:	**Deep infection**: A deep infection was defined by the Musculoskeletal Infection Society criteria using laboratory values (complete blood count, erythrocyte rate, sedimentation rate, and C-reactive protein), purulent drainage from the surgical incision, or positive microbiology from a knee aspiration per the 2 senior surgeons.
CANCIENNE 2015	Deep Periprosthetic Joint and wound infection	**Deep periprosthetic infection** determined by hospital readmission with a procedure for infection with proximity to the joint Wound infection defined as superficial infection 29]. A superficial infection was defined as any wound infection that involved only the skin and subcutaneous tissue

Table 4 summarising the infection rate for patients in the included studies that received a steroid injection within different time intervals prior to surgery, compared to all individuals in the included studies that did not receive steroid injections prior to surgery. The odds ratio for each strata compared to the group who did not receive an injection is also shown in the table, along with a confidence interval and test for the hypothesis that the odds ratio is equal to 1, computed using Fisher's exact test. In the columns below the two groups, the percentage (and number in parentheses, plus the total number in the group) of the participants who have contracted an infection is stated.

In the column named OR, the odds ratio is stated, which describes the difference in the two groups. If the odds ratio is greater than 1, it is more likely to get an infection if you have had an injection. The last column where the p-value is written is a formal test for whether OR = 1. If $p < 0.05$, the confidence interval for OR will not overlap 1, which is the case for all the groups here, and this is what is meant when one says that the test result is 'significant'.

Table 4: The rate of postoperative infection stratified by preoperative injection timing

	Injection	No injection	*p*-Value	OR (95% CI)
0–2 mo	2.21% (408/18,468)	1.15% (4,979/331,175)	< 0.001	1.47 (1.32, 1.63)
2–4 mo	2.27% (541/23,817)	1.15% (4,979/331,175)	< 0.001	1.51 (1.38, 1.65)
4–6 mo	1.94% (280/14,436)	1.15% (4,979/331,175)	< 0.001	1.29 (1.14, 1.46)
6-8 mo	2.15% (203/9,453)	1.15% (4,979/331,175)	< 0.001	1.43 (1.23, 1.65)
8-10 mo	2.14% (204/9,527)	1.15% (4,979/331,175)	< 0.001	1.42 (1.23, 1.64)
10-12 mo	2.15% (204/9,477)	1.15% (4,979/331,175)	< 0.001	1.43 (1.23, 1.65)

In the above table, some individuals will be counted more than once, due to the fact that the different reported time windows in the data only partially correspond to the two-month time-windows we consider here. To compensate for this, we can try to weight the observations by the proportion of the time window per observation that intersects each two-month window in the table. The resulting table is given below, where the confidence intervals and p-values are computed in the same way as above.

There is an increase in percentage of 1% among the participants in the injection group compared to no-injection group. The percentage is slightly similar throughout the different time intervals with small variation. This indicates that the post - operative infection rates conditional on whether a preoperative injection is performed are quite similar across the different time - periods. The difference between the conditional infection rates is significant.

Table 5: The rate of postoperative infection stratified by preoperative injection timing

	Injection	No injection	*p*-Value	OR (95% CI)
0–2 mo	2.08% (332/15,945)	1.15% (4,979/331,175)	< 0.001	1.38 (1.23, 1.55)
2–4 mo	1.96% (226/11,528)	1.15% (4,979/331,175)	< 0.001	1.30 (1.13, 1.49)
4–6 mo	1.83% (198/10,814)	1.15% (4,979/331,175)	0.008	1.22 (1.05, 1.41)
6-8 mo	2.15% (68/3,168)	1.15% (4,979/331,175)	0.005	1.43 (1.10, 1.82)
8-10 mo	2.14% (68/3,176)	1.15% (4,979/331,175)	0.006	1.42 (1.10, 1.81)
10-12 mo	2.14% (68/3,184)	1.15% (4,979/331,175)	0.007	1.42 (1.10, 1.81)

In Table 4, we weight the different patients that partially overlap with two or more of the time intervals, by the proportion that the reported time - period that the patient received an injection within that overlaps with each time - window. I.e., if one patient in a study received an injection between 6-12 weeks before the operation, we would count this as 1 / 3 of a patient in the 2-4 month group, and 2 / 3 of a patient in the 4-6 month group, instead of one whole patient in both groups as we did in Table 5.

As the injected patients are now not over-counted, one would think that these p-values and confidence intervals are more representative of the uncertainty in the data, although the qualitative interpretation does not change compared to before, as the point - estimates are relatively similar, and the odds ratio is still significantly greater than zero for each group.

Table 4 is also illustrated in figure 5, shown below, where the odds ratio, and the 95 % confidence intervals are drawn. The figure was produced, and computations done using R.

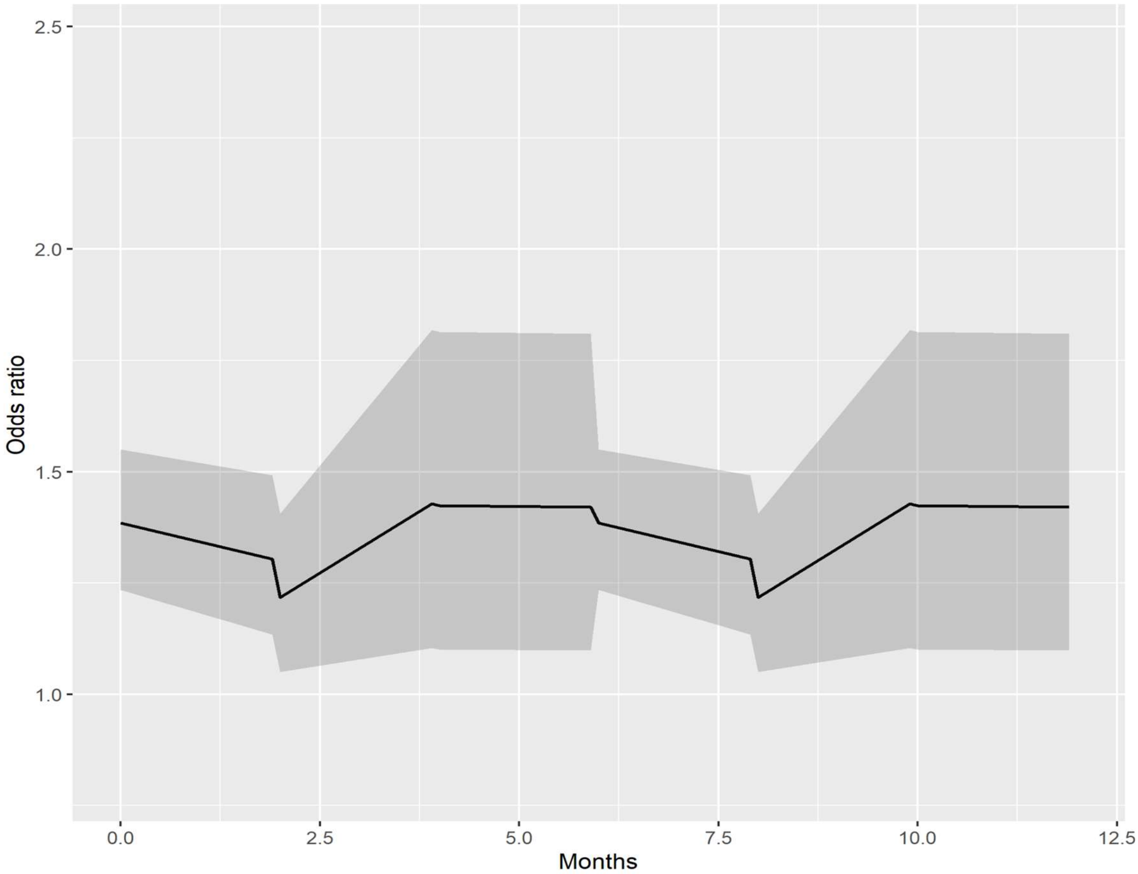

Figure 2: Graphic illustration of the odd ratio as a function of time with the 95% confidence intervall ollustrated as shadowed area that extends above and below of the horizontal line.

Number of patients who got an infection n=961 out of all the patients that got an injection n=46910. Number of patients who got an infection n=4979 in the controll group that didn not get an injection of the total number of pasients in the no-injection group n=326196.

Table 6: Illustration of the number of patients in the injection and no-injection group that had an postoperative infection.

	Injection	*No injection*
Infection	961	4979
No infection	46910	326196

The formal test for whether there is a difference is significant, with a p-value almost zero. An interesting number that is easy to interpret is the 'Number needed to harm', which in this case is 198, with a 95% confidence interval [149, 248]. This number is the number of patients you have to treat (give an injection before the operation) on average before you get an extra patient with an injection who would not have gotten an infection without the injection.

Another way of describing this is that if you give 198 patients an injection before the operation, and 198 patients no injection, and repeat this very many times, there will be on average one more case of infection in the group that received the injection.

Discussion

The current study and type of analysis executed in this study has attempted to give an overall impression of infection/no infection and has included all type of joint. To my knowledge this is the first study to register an infection/no-infection analysis across all joints.

There is a 1% increased rate of infection in the injection group compared to controll which seem to be in accordance to previously reported rate (Jämsen et al., 2010; McIntosh et al., 2006; Pulido et al., 2008). The percentage is slightly similar throughout the different time intervals indicating that the post - operative infection rates conditional on whether a preoperative injection is performed. The difference between the conditional infection rates is significant. The incidence of infection of surgical site following arthroplasty in England have been shown to vary from 0.2-1.1% (Blom et al., 2003), while the Danish Hip Arthroplasty register have concluded with a 0.7% of 80 756 total hip arthroplasties that needed revision due to infection (Pedersen et al., 2010). The percentage of infection in this study is slightly similar throughout the different time intervals up to 12 months and in accordance to other studies (Kaspar & De, 2005b; Papavasiliou et al., 2006). Papavasilious and Kaspar registered infection rates up to respectively 11 and 12 months postoperatively. Other studies has shown increased infection rates up to 24 months (Ravi et al., 2013). Ravi found a significantly increased odds ratio (2.24, $p = 0.0003$) of revision THA within two years in those who had an intraarticular corticosteroid injection within six months of THA (22/986; 2.2%) compared with patients who did not have a steroid injection in the same six-month period (31/2958,1.05%) ($p = 0.005$).

There is not definitive consensus on the time steroids remain active intra-articulately, but there is data to suggest that no soluble intra-articular steroids can remain inactive in the joint and be reactivated months later at the time of surgery (Papavasiliou et al., 2006). In addition low grade deep infection is often diagnosed later than one year after total hip arthroplasty and therefore studies assessing steroids and post-operative infection rates with only one year follow-up or less may have underestimated the true infection rates (Marsland et al., 2014).

Number of patients who got an infection are n=961 out of all the patients that got an injection n=46910. Number of patients who got an infection n=4979 in the controll group that didn't not get an injection of the total number of patients in the no-injection group n=326196. Number needed to harm in this case is 198, with a 95% confidence interval [149, 248].

In this current systematic review 6/7 of the included studies has accounted for or excluded patients with higher infection risk due to comorbidities. Only 1/7 studies has accounted for patients on immunosuppressive medication (Kaspar & De, 2005b). The number of comorbidities the studies have accounted for and the discrepancy of the variables however vary between the studies.

Bhattacharjee (Bhattacharjee et al., 2021) accounted for several other risk factors such as sex, age, chronic kidney disease, chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes, hypertension, ischemic heart disease, obesity, osteoarthritis, pulmonary heart disease, rheumatoid arthritis, tobacco, but not immunosuppressive medication (Bhattacharjee et al., 2021). The author found an overall infection rate being significantly higher in the injection group that the cohort group, and additionally a further increase of the infection rate for patient with underlying comorbidities (aged older than 65 years (0.91%; P , 0.001), of female sex (0.92%; P = 0.017), with COPD (1.45%; P , 0.001), with diabetes (1.19%; P , 0.001), with hypertension (1.01%; P = 0.003), with ischemic heart disease (1.37; P , 0.001), with obesity (1.48%; P , 0.001), with pulmonary heart disease (1.66%; P = 0.002), with rheumatoid arthritis (1.68%; P , 0.001), and tobacco (1.42%; P , 0.001)).

Meermans (Meermans et al., 2012) accounted for similar comorbidities showing similar results as Bhattacharjee (Meermans et al., 2012). In addition Meermans accounted for the effect of immunosuppression medication on the infection rate.

Cancienne in to separate studies (Cancienne et al., 2019; Cancienne et al., 2015b) and Lee (Lee et al., 2022) accounted for age, gender, obesity, smoking status and diabetes and found an increased incidence of infection, respectively for each author, at 2 weeks, 4 weeks and within 3 months for the injection group compared to control group. Furthermore it was seen an additional increase for patients with comorbidities (Cancienne et al., 2019; Cancienne et al., 2015b; Lee et al., 2022).

Schairer (Schairer et al., 2016a) did not account for immunosuppressive but accounted for the other comorbidities in addition to socioeconomic status based on income (Schairer et al., 2016a). It was concluded with an 50% increase in the infection rate when injection was performed within 3 months' timeframe. Comorbilities account for further increase in the infection rate. Amin (Amin et al., 2016) didn't account for or excluded based on any comorbidities, in addition to certain types of infection such as superficial incisional infections, which involved the skin, and/or subcutaneous tissue.

Lifestyle and socioeconomic seem to be a contributing factor for increased infection rate and the degree of which the included studies has accounted for vary a lot (Chan et al., 2013). Obesity and use of tobacco have been addressed by all except one study (Amin et al., 2016), while income has only been addressed by Schairer (Schairer et al., 2016a). BMI is registered to be a contributor for increased risk of infection. In particular a BMI of more than 35 kg/m2 is associated with an increased rate of positive intra-operative cultures and prosthetic joint infections (Font-Vizcarra et al., 2011) while a BMI more than 40 kg/m2 is associated with a higher rate of revision for sepsis following total hip arthroplasty (McCalden et al., 2011).

Protocols regarding use of antibiotics preventively preoperatively play an important role in reducing the prevalence of infection rate postoperatively (Tyllianakis et al., 2010). Future studies should provide information regarding use or no-use of prophylactic use of antibiotics preoperatively, and systematic reviews should account for the use of such protocols.

It is of importance that more explicit exclusion criteria and higher degree of agreement regarding comorbidities to account for is included in future studies. Patients at higher risk of infection can affect the results regarding patients at higher risk of infection are considered in future studies. In this study, I weight the different patients that partially overlap with two or more of the time intervals, by the proportion that the reported time - period that the patient received an injection within that overlaps with each time - window. I.e., if one patient in a study received an injection between 6-12 weeks before the operation, I would count this as 1 / 3 of a patient in the 2-4-month group, and 2 / 3 of a patient in the 4-6-month group, instead of one whole patient in both groups as I did in Table 2. Future studies should have shorter time intervals measured in order to make the number of participants easier to compare in-between groups in systematic reviews.

Limitation of the study

The current study is an infection – no infection design and doesn’t take into consideration underlying comorbidities of the patients. The difference between the groups should be interpreted with caution as the results can be due to confounding factors, in particular systematic difference between injection and no-injection groups which can make the injection group have an increased risk of infection that it would have happened even in the absence of the injection (Li et al., 2022). Such confounding factors have been mentioned and analysed previoulsy under the comorbidities i.e metabolic diseases such as diabetes and cardiovascular disorders.

Conclusion

Despite the fact that systematic reviews are considered to be the golden standard of scientific evidence, the plethora of systematic reviews published on this topic have concluded with conflicting results.

The evidence suggesting that patients who receive steroid injections prior to joint arthroplasty are at increased risk of post-operative infection is at 1% with a number to harm measured to 198. There is no obvious correlation with timing other than infection rates are slightly similar throughout a 12 months' period and corresponds to the time interval for cortisone to dissolve and in accordance to other studies.

In the present study, the best available evidence suggested that steroid injections prior to arthroplasty indicates that the post - operative infection rates conditional on whether a preoperative injection is performed are quite similar across the different time - periods.

The strength of recommendation is limited to the limitations of current evidence and results should be interepreted with caution due to confounding factors and comorbilities that havent been addressed in the current study. In conclusion, the literature is scarce and the level of evidence is still not sufficient to cover the complexity of the topic.

Based on the limitations of the current available literature, it is of importance to state that future studies should focus on multicentre trials with large number of patients, agreement on type of infections, limitations and methodological challenges should be addressed to improve future study executions and to provide conclusive evidence on this question.

Based on the existing literature, it is of importance that good communication regarding previous intra-articular corticosteroid injections is established between clinical physiotherapist, general practitioner's rheumatologists and orthopaedic surgeons when joint arthroplasty is being considered. Orthopaedic surgeons should show caution to joints previously exposed to corticosteroid injections and map underlying comorbidities in order to take a final decision in regards to any residual effects of the steroid injection lasting up to 11 months. Informative communication with the patient with inclusion in the decision making, patients preference and caution based on the limitation of the data in addition to underlying comorbidities, decision can be made between surgeons and patients.

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