Does Previous Intra-Articular Steroid Injection Increase the Risk of Joint Infection Following Total Hip Arthroplasty or Total Knee Arthroplasty? A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Joint infection might be one of the rare but serious complications following a total knee or hip arthroplasty (TKA, THA). A previous intra-articular steroid injection was considered as a risk factor. The purpose of present study was to access the effects of ipsilateral intra-articular steroid injection followed by TKA or THA on the incidence of infections later.

Material/Methods: Clinical studies reporting infection in THA or TKA after previous injection of intra-articular steroid were identified from the online database of PubMed, Embase, the Cochrane Library, and additional manual searches until July 2013. The pooled effects were measured by risk difference (RD), together with 95% confidence intervals (CIs).

Results: A total of 11 related studies met our inclusion criteria. The final meta-analysis investigated 6 clinical studies designed as retrospectively created cohort studies with control groups, involving 1474 participants reporting 14 deep infections and 72 superficial infections. Compared with the control group, there was no significantly increased rate of infection among the participant with steroid injection prior to THA or TKA, with corresponding RD (95% CIs) of 0.01 (–0.01, 0.02) for deep infection, 0.01 (–0.02, 0.03) for superficial infection, and 0.02 (–0.02, 0.07) for total infection. The data from 3 prospective studies without control groups and 2 case-control studies were consistent with the results of our meta-analysis.

Conclusions: No increased risk of infection among patients who received steroid injections prior to the surgery was identified from the present evidence. A multicenter prospective study with more defined variables is needed further investigate this issue.

MeSH Keywords: Arthroplasty, Replacement, Hip • Arthroplasty, Replacement, Knee • Bacterial Infections • Injections, Intra-Articular • Meta-Analysis

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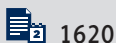
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Background

Steroid treatment for the management of pain in arthritic joints or osteoarthritis has been supported by a number of randomized clinical trials and meta-analyses [1–3]. However, adverse effects have been reported with the use of steroids, such as septic arthritis [4] and articular cartilage deterioration [5]. Findings from some studies indicated that joint infection following intra-articular steroid injections might be one of the rare but serious complications of intra-articular steroid injection. A study by Papavasiliou et al. indicated that intra-articular steroid injections prior to total knee arthroplasty are associated with increased incidence of infections, which elicited critical comments [6]. Most other studies showed no evidence that use of intra-articular steroid altered the incidence of deep infections following total hip or knee arthroplasty (THA or TKA) [7,8]. Until now, the data regarding the relationship between the risk of joint infection following a TKA or THA and a previous intra-articular steroid injection were inconsistent. The low incidence of the infection demands large-sample clinical studies to identify the effect of intra-articular steroid injection on the risk of infections. We therefore attempted a synthesis of the available clinical evidence under an updated meta-analysis to determine the association between intra-articular steroid injection and risk of joint infection.

Material and Methods

Eligibility criteria

Clinical studies that compared the intra-articular steroid injection prior to THA or TKA with a control group were eligible for inclusion. Eligible outcomes included infections, deep infections, and superficial infections. We included studies irrespective of language, publication status, and patient age. Exclusion criteria were studies in animals, without major end points.

We searched PubMed, Embase, and the Cochrane Library using predefined text words related to the operation (e.g., "total hip replacement" or "total knee replacement" or "hip arthroplasty" or "knee arthroplasty"), injection (e.g., "intra-articular" or " steroid"), and infection. Relevant studies without a control group were also included in the present study for providing more evidence to achieve the final results. We also manually screened the references of the included studies and pertinent systematic reviews. The electronic literature search was last updated July 2013.

Two authors (Qianqian Wang and Xu Jiang) independently reviewed all titles and full text of the relevant studies. Disagreements were resolved through discussion.
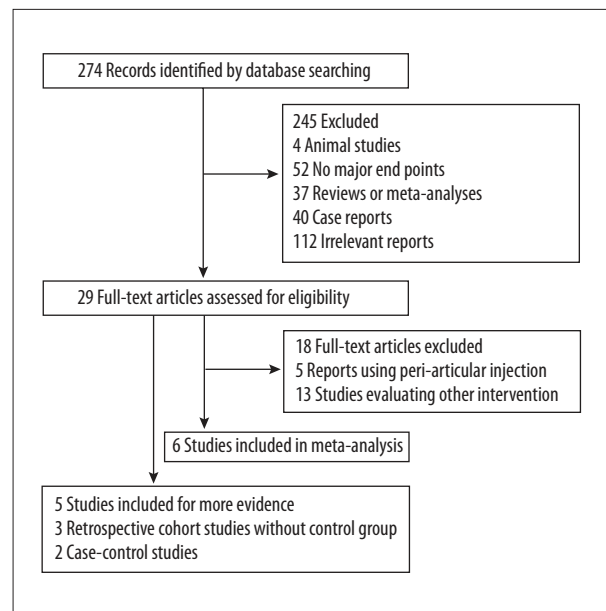

Figure 1. Flow chart showing the selection process of studies for analysis with specifications of reasons.

Data extraction

The following items were extracted from each study: authors, publication year, study design, per-group sample size, conditions of performing injection, population characteristics, and the number of infection in each group. Data extraction was performed independently by 2 reviewers.

Statistical analysis

The principal measure was absolute risk difference (RD). The RD estimates and corresponding 95% confident intervals (CIs) for the assessed outcomes were calculated for each trial. We summarized RD estimates using a random-effects model. Fixed-effects models assume that there is a common underlying effect and that the variability observed is attributed to chance alone, whereas random-effects models acknowledge that true between-study heterogeneity exists and its calculations take into account the presence of heterogeneity. In the absence of heterogeneity, fixed- and random-effects models yield the same results. The evidence of statistically significant heterogeneity was assessed by Q statistic and the extent of the observed heterogeneity was assessed by the I^2 (ranging from 0% to 100%) [9].

For detecting publication bias, we assessed the small study effect by using the Egger's test. In addition, the trim-and-fill approach was used to obtain an adjusted effect size that takes into account publication bias [10]. We also performed a cumulative meta-analysis to assess the evolution of the observed effects over time.

Table 1. The characteristics of the matched cohort study for meta-analysis.

Study	Publish year	Country	Design	Location	Sample size	Place	Provider	Duration between injection and replacement	Dosage of injection
Kaspar et al. [11]	2005	Canada	Retrospective, matched, cohort study	Hip	80(50/30)	Fluoroscopy suite	Radiologist	NR	Injection of 80 mg of methylprednisolone (Depo-Medrol; Pharmacia Upjohn), which was usually mixed with 1 ml to 5 ml of bupivacaine
McIntosh et al. [12]	2006	USA	Retrospective matched cohorts	Hip	448(185/263)	Radiology department	Radiologist	112days	20.47 mg (6–40 mg) steroid
Sreekumar et al. [13]	2007	UK	Retrospectively created matched cohorts	Hip	202(47/155)	Radiology suite	NR	11months	Depomedrone 2 ml (Depomedrone 40 mg/ml, Pharmacia) and Chirocaine (5 mg/ml)
Meermans et al. [14]	2012	Belgium	Retrospectively created matched cohorts	Hip	350(98/252)	Operating theater	Surgeon	155 days	Combination of 80mg methylprednisolone (Pfizer, Elsene, Belgium) and between 1 and 3 mL (5–15 mg) levobupivacaine
Papavasiliou et al. [6]	2005	UK	Retrospective study	Knee	144	NR	NR	NR	NR
Desai et al. [8]	2009	UK	Matched cohort study	Knee	250(100/150)	Operating theatre	NR	NR	Depomedrone 2 ml (Depomedrone 40 mg/ml Pharmacia, Surrey, U.K.) and Chirocaine (5 mg/ml, Abbott, Maidenhead, U.K.)

UK – United Kingdom; NR – not report.

We further assessed potential associations of the treatment effect with study-level variables in the subgroup analyses and meta-regression analysis. Prespecified subgroups analyses were performed based on the surgery positions (knee *vs*. hip).

All analyses were performed in Stata 9.0 (StataCorp). All *p* values are 2-sided. Statistical significance was assumed at a *p* value threshold of 0.05.

Results

Of 226 articles identified, only 6 articles involving 1474 participants totally reporting 14 deep infections and 72 superficial infections were included in the meta-analysis [6,8,11–14] (Figure 1). There were no randomized controlled trials and all of the 6 studies were retrospectively created matched cohorts design. All of the participants were of Caucasian race. Four of the studies were conducted in patients with total hip arthroplasty [11–14] and the other 2 were in patients with total knee arthroplasty [6,8]. The sample size ranged from 80 to 448. The mean age of the population varied from 63.6 years to 70.8 years. We also extracted the information about the injection operation for each study. From the available data, injection could be performed in an operating theatre or in a radiology department by a radiologist or surgeon. The mean duration between injection and replacement ranged from 112 days to 11 months. The main study characteristics are listed in Table 1.

Compared with the control group, there was no significant increased rate of deep infection among the participant with steroid injection prior to THA or TKA, with corresponding RD (95%
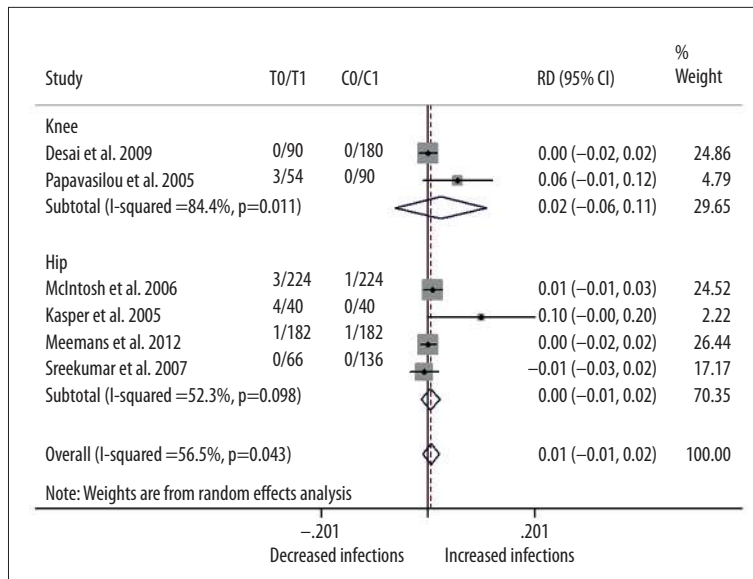
Study	T0/T1	C0/C1	RD (95% CI)	% Weight
Knee				
Desai et al. 2009	0/90	0/180	0.00 (−0.02, 0.02)	24.86
Papavasilou et al. 2005	3/54	0/90	0.06 (−0.01, 0.12)	4.79
Subtotal (I-squared =84.4%, p=0.011)			0.02 (−0.06, 0.11)	29.65
Hip				
McIntosh et al. 2006	3/224	1/224	0.01 (−0.01, 0.03)	24.52
Kasper et al. 2005	4/40	0/40	0.10 (−0.00, 0.20)	2.22
Meemans et al. 2012	1/182	1/182	0.00 (−0.02, 0.02)	26.44
Sreekumar et al. 2007	0/66	0/136	−0.01 (−0.03, 0.02)	17.17
Subtotal (I-squared =52.3%, p=0.098)			0.00 (−0.01, 0.02)	70.35
Overall (I-squared =56.5%, p=0.043)			0.01 (−0.01, 0.02)	100.00
Note: Weights are from random effects analysis				

−.201 Decreased infections   .201 Increased infections

Figure 2. Meta-analysis for the relationship between previous intra-articular steroid injection and deep infection rate following THA or TKA. The diamonds are shown as overall effect, calculated by risk difference (RD) in a random-effects model. T0 is number of deep infections in the injection group; T1 is total number of patients in the injection group; C0, number of deep infections in the group without injection; C1, total number of patients in the group without injection.
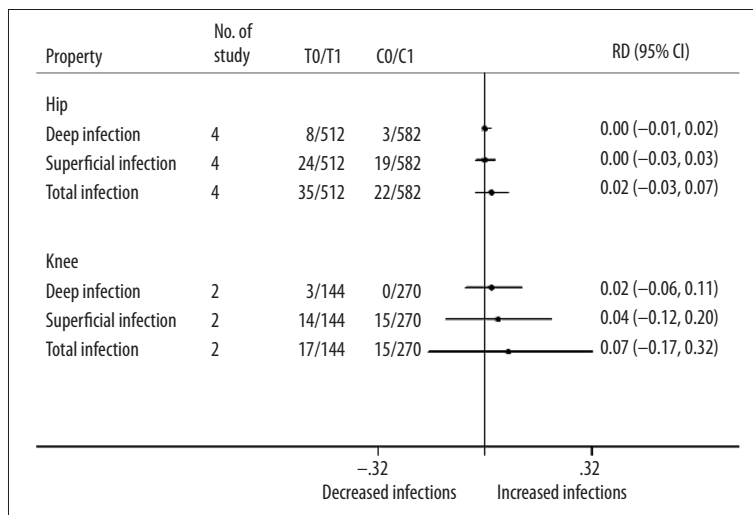
Property	No. of study	T0/T1	C0/C1	RD (95% CI)
Hip				
Deep infection	4	8/512	3/582	0.00 (−0.01, 0.02)
Superficial infection	4	24/512	19/582	0.00 (−0.03, 0.03)
Total infection	4	35/512	22/582	0.02 (−0.03, 0.07)
Knee				
Deep infection	2	3/144	0/270	0.02 (−0.06, 0.11)
Superficial infection	2	14/144	15/270	0.04 (−0.12, 0.20)
Total infection	2	17/144	15/270	0.07 (−0.17, 0.32)

−.32 Decreased infections   .32 Increased infections

Figure 3. Meta-analysis for the relationship between previous intra-articular steroid injection and infection rate following surgery stratified by location (hip or knee). The diamonds are shown as overall effect, calculated by risk difference (RD) in a random-effects model. T0 is the number of deep infection in the injection group; T1 is the total number of patients in the injection group; C0, number of deep infection in the group without injection; C1, total number of patients in the group without injection.

CIs) of 0.01 (−0.01, 0.02) (Figure 2). Similar trends were also observed with the other endpoints and the RD (95% CIs) was 0.01 (−0.02, 0.03) for superficial infection and 0.02 (−0.02, 0.07) for total infection. The results were not changed materially after being classified by the injection site (Figure 3).

Presence of publication bias was not identified by Egger's test in all of the analyses (data not shown).

We also summarized the relevant data from a cohort study without matched a control group. Three studies were identified from the databases [7,15,16]. The mean time intervals from the infection to the joint replacement were 18.0 months for the study by Chitre, 12.1 months for the study by McMahon and 6.2 months for the study by Sankar. The mean follow-ups were 25.8 months, 97.8 months, and 23.2 months, respectively. All of the 3 studies observed 1 superficial infection during their follow-up

period. One deep infection occurred in McMahon's study, but the author argued that deep-wound infection of that patient was probably not related to the previous steroid injection due to confounding factors. There were 2 case-control studies that included patients with evidence of deep infection following total knee arthroplasty and controls without clinical or radiological evidence of infection in the knee after total knee replacement arthroplasty [17,18]. No significant difference of injection rate was found between the 2 groups in either of the 2 studies. The characteristics of these 5 studies are displayed in Table 2.

Discussion

No evidence of increased rates of deep or superficial infection was identified from the meta-analysis. Furthermore, neither the results from case-control studies nor the findings from observational

Table 2. The characteristics of the prospective studies without control group and case-control studies.

Study	Publish year	Country	Design	Location	Sample size	Mean age of the patients	Duration between injection and replacement	Place	Provider	Dosage of injection	Mean follow-up (months)	No. of deep infection	No. of superficial infection
Chitre et al. [7]	2007	UK	Retrospective cohort	Hip	36	63.7 (30~83)	18 (4~50) months	Operation theatre	Surgeons	A combination of 80 mg depomedrone and between 1 ml and 5 ml 0.5% bupivacaine	25.8 (9~78)	0	1
McMahon et al. [15]	2012	UK	Retrospective cohort	Hip	49	69.0 (51~98)	12.1 (5.1~19) months	Laminar flow theatre with fluoroscopy guidance	Surgeons	80 mg depomedrone and 5 ml of 0.5% bupivacaine	97.8 (85~117)	1	1
Sankar et al. [16]	2012	UK	Retrospective cohort	Hip	40	68.4 (52~82)	6.2 (2~23) months	Orthopaedic laminar flow theatre	Surgeons	A mixture of 80-120 mg of depo-methyl prednisolone and 8-10 ml of 0.5% Bupivacaine into the joint	23.2 (11~37)	0	1
Joshy et al. [17]	2006	UK	Case-control	Knee	64	69.5	NR	NR	NR	NR	46 (12~121); 33 (8~56)	McNemar's test ------- p=1	
Horne et al. [18]	2008	New Zealand	Case-control	Knee	247	NR	NR	NR	NR	NR	NR	OR (95%CIs) ------- 1.38 (0.55, 3.31)	

UK – United Kingdom; NR – not report.

cohort studies supported the hypothesis that steroid injection prior to THA or TKA increased the risk of deep infection.

The incidence of deep infection after total hip or knee arthroplasty is remarkably low, with an infection rate of less than 1%. However, the consequences of deep infection are severe and further surgery is required, often resulting in 2-stage revision surgery. Steroid injection has been considered to be a risk for infection following total hip or knee arthroplasty. A significant increase in the incidence of deep infection in hip or knee replacement following steroid injections was reported by 2 studies that differed from most previous studies. Kaspar et al. [11] performed a retrospective cohort study including 40 patients who had received an injection before THA and 40 matched controls who had not, reporting that 10% of the injection group developed deep infection compared with 1% in the control group. Papavasiliou et al. compared 54 knees with an injection prior to knee replacement to a control group of 90 knees without injection before knee replacement [6]. Three deep infections were observed in the patients with previous steroid infiltration whereas none were reported in the control group. One explanation of the results from the author was that some of the steroid crystals did not fully dissolve within the knee joint but remained within the surrounding soft tissues or cystic areas of degeneration within

the knee, and at the time of the operation the steroid crystals might be released from these places. However, the results of that paper have been debated in the comments about variable time and numbers of injections prior to surgery, different type of prosthesis, and lack of consideration of operating conditions and surgery.

The present meta-analysis combined all the data about this issue and has greater power to explore the real influence of intra-articular injection of steroids on deep infection. However, the results should still be cautiously interpreted since some limitations. First, all the studies included for analyses were retrospectively designed, thus the confounding factors, such as injection procedure and characteristics of the patients, could not be well controlled. There were a number of variables that might lead to bias, such as a different operating surgeon in each study, variable time intervals between injection and surgery, and different total numbers of injections prior to surgery. Most of the studies did not report this information, which prevents us from evaluating the effects on the association. Other risk factors for infection such as diabetes, poor nutrition, renal failure and hypothyroidism should be considered [19,20]. Second, the incidence of infection is very low, and it might still be too underpowered to rule out a significant increase in infection rate in the patients injected.

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Conclusions

In conclusion, no significant increase of infection among patients injected with steroid prior to the surgery was identified from the present evidence. A multicenter prospective study with more defined variables or pooled analyses with individual-level data will help resolve this issue.

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