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# Do prior intra-articular injections impact on the risk of periprosthetic joint infection in patients undergoing total hip arthroplasty? A meta-analysis of the current evidences with a focus on the timing of injection before surgery

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- *Purpose:* Intra-articular injection is a well-established and increasingly used treatment for the patient with mild-to-moderate hip osteoarthritis. The objectives of this literature review and meta-analysis are to evaluate the effect of prior intra-articular injections on the risk of periprosthetic joint infection (PJI) in patients undergoing total hip arthroplasty (THA) and to try to identify which is the minimum waiting time between hip injection and replacement in order to reduce the risk of infection.
- *Methods:* The database of PubMed, Embase, Google Scholar and Cochrane Library was systematically and independently searched, according to Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) guidelines. To assess the potential risk of bias and the applicability of the evidence found in the primary studies to the review, the Newcastle–Ottawa scale (NOS) was used. The statistical analysis was performed by using the software 'R' version 4.2.2.
- *Results:* The pooling of data revealed an increased risk of PJI in the injection group that was statistically significative ($P = 0.0427$). In the attempt to identify a 'safe time interval' between the injection and the elective surgery, we conducted a further subgroup analysis: in the subgroup 0–3 months, we noted an increased risk of PJI after injection.
- *Conclusions:* Intra-articular injection is a procedure that may increase the risk of developing periprosthetic infection. This risk is higher if the injection is performed less than 3 months before hip replacement.

**Keywords**

- intra-articular injections
- hyaluronic acid
- corticosteroids
- periprosthetic joint infections
- hip infection
- osteoarthritis
- total hip arthroplasty

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## Introduction

Osteoarthritis (OA) is a degenerative disease that affects joints, especially hip and knee. Population aging leads to a progressive increase in the incidence of this disease. Half of the world's population aged 65 and older suffer from OA and 80% of people with symptomatic OA have limitations in movement, while 25% cannot perform their normal daily activities (1). The *European Project on Osteoarthritis* (EPOSA) has made it possible to obtain more accurate demographic data on the disease, involving six European countries, recording that the prevalence of OA is 30.4% (2).

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Hip OA involves worsening groin pain and progressive reduction of joint excursion, leading to a significant deterioration in the quality of life and daily activities. The natural history of OA goes through various phases, more or less symptomatic, which last for years, at the end of which the only resolving treatment is the prosthetic replacement of the joint (3).

Nonoperative treatment for hip OA consists of a stepwise approach. This approach includes weight loss, activity modification, physiotherapy, oral analgesics including nonsteroidal anti-inflammatories, and intra-articular injections. Less invasive surgical options, such as arthroscopy, have very narrow indications in patients with OA (4).

Intra-articular injection is a well-accepted treatment for the patient with mild-to-moderate OA who has exhausted other noninvasive treatment options. Hip injection should always be performed under visualization of the joint by x-rays or ultrasound. It can also be performed with different types of medication: hyaluronic acid (HA), platelet-rich plasma (PRP), HA and PRP, corticosteroids (CS) and local anaesthetics (LA) (5, 6).

The infiltrative treatment may be ineffective in reducing pain and improving function (7). Therefore, it is necessary to propose a total hip arthroplasty (THA) to the patient. Nowadays, the correct timing between the last intra-articular hip injection and THA is unknown. In fact, this 'safety' time interval between the two procedures is essential to minimize the risk of periprosthetic joint infection (PJI) due to possible contamination during the previous hip injections.

The primary objectives of this literature review and meta-analysis are to evaluate the effect of prior intra-articular injections on the risk of PJI in patients undergoing THA and to try to identify a minimum waiting time interval between hip injection and replacement in order to reduce the risk of infection. The secondary objective is to evaluate the type of medication and their relative risk on the rate of PJI.

## Materials and methods

This literature review and meta-analysis were performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) statement guidelines (8).

### *Search strategy and information sources*

The database of PubMed, Embase, Google Scholar and Cochrane Library was systematically and independently searched until 15 December 2022 by two reviewers (MS and VC). The details of the literature search are reported in the Supplementary material section. Additional studies were eventually identified from the references of the retrieved papers.

### *Eligibility criteria*

The inclusion criteria for the retrieved studies are as follows:

- Population: patients older than 18 years undergoing THA.
- Intervention: intra-articular injections of any drugs performed before the THA surgical procedure.
- Comparison: a cohort of patients who did not undergo intra-articular injections prior to the THA surgical procedure.
- Outcome: diagnosis of PJI (according by any definition used in the included studies).
- Study type: all cohort studies, random and clinical controlled trials, prospective or retrospective.

The exclusion criteria adopted were

1. Absence of a control group;
2. Studies in which it was not possible to retrieve the incidence of PJI in each arm;
3. Studies not written in the English language;
4. Studies with duplicated data.

### *Study selection*

Two reviewers (MS and VC) independently evaluated the studies for eligibility. Once the relevant studies were identified, their full text wasextracted and selected on the base of the inclusion and exclusion criteria. In case of disagreement, the senior authors (GS and GL) were sought to resolve the divergences.

### *Data extraction*

Two reviewers (MS and VC) performed the data extraction independently. In case of disagreement, the senior authors (GS and GL) were sought to resolve the divergences. Data extracted from the eligible studies included first author names, year of publication, study design, study location (country), sample size, number of infected and non-infected patients in each cohort, mean age, the drugs injected, time from injection to surgery, the reference standard of PJI diagnosis and duration of follow-up.

### *Quality evaluation*

Two reviewers (MS and VC) performed the data extraction independently. In case of disagreement, the senior author (GL) was sought to resolve the divergences. To assess the potential risk of bias and the applicability of the evidence found in the primary studies to the review, the Newcastle–Ottawa scale (NOS) was used (9).

### *Statistical analysis*

The statistical analysis of this meta-analysis was performed by using the software 'R' version 4.2.2 (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

A random-effects model was used to perform the meta-analysis, on the basis of the sparse nature of data and because we anticipated considerable between-study heterogeneity.

The meta-analytical methodology was

- Mantel–Haenszel (MH) method for pooling data. MH method is specific for binary outcomes and was proposed for the common odds ratio in a stratified case–control study (10) and then extended to the risk ratio (RR) and risk difference as a measure of treatment effect for sparse data by Greenland and Robins (11).
- The Paule–Mandel estimator was chosen for calculation of $\tau^2$ (12).
- We used Knapp–Hartung adjustments (13) to calculate the confidence interval (CI) around the pooled effect. Several studies (14, 15) showed that these adjustments can reduce the chance of false positives, especially when the number of studies is small.
- Continuity correction of 0.5 in studies with zero cell frequencies was used only to calculate individual study results (16).

The pooled incidence of PJI was reported using RR with 95% CIs.

Forest plots were used to display the RR of PJI for each study, displaying heterogeneity statistics as well.

A L'Abbé plot (17) was also drawn to allow an easy and direct visualization of the summary measure of the risk of PJI and of the level of heterogeneity.

The heterogeneity was evaluated using Higgins and Thompson's $I^2$ statistics (18), and Q-profile method was used for CI of $\tau^2$ and $\tau$ (19). Prediction intervals were furthermore provided to better clarify the meaning of the heterogeneity measure reported (20).

The potential sources of heterogeneity were investigated as follows:

- Checking for outliers and influential cases by performing an influence diagnostic (21). A Baujat plot was used to report the influence diagnostic (22). After we identified the influential studies, we performed and reported the results of a sensitivity analysis in which these studies are excluded.
- Performing a sub-group analysis based on the timing of injection before THA, in an attempt to reduce the potential cause of heterogeneity.
- Investigating the Publication Bias (PB) using Funnel Plots (when the *P* value was <0.05, the test for PB was considered statistically significant) and the Egger's test (23).

## Results

### *Search and selection process*

The search strategies are reported in Supplementary Table 1 (see section on supplementary materials given at the end of this article) in the Supplementary material section, and the study flow chart is reported in Fig. 1. The process of literature search yielded 5538 articles, from which we removed 1500 records because they were duplicates and 3200 records for other reasons (e.g. other languages and not pertinent). After this first process, the remaining 838 papers were screened by evaluating titles and abstracts. At the end of the screening process, the full text of 30 articles was assessed for eligibility. Nineteen papers were excluded for several reasons (tenarticles reported cumulative data for hip and knee joints, three papers compared different numbers of injections and six articles did not have a control group). Finally, 11 papers were included in this systematic review (24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34). One study (28) was not included in the meta-analysis because, reporting no events for each arm, it did not provide any information for pooling data and was not indicative for the meta-analytic strategy.

### *Included studies characteristics*

The details of the studies included in this systematic review are reported in Table 1. All papers were published from 2005 to 2021. Three studies were conducted in Europe (26, 27, 32), three in Canada (24, 28, 29) and the remaining five studies in USA (25, 30, 31, 33, 34). All studies were retrospective, six adopted a matched cohort design (24, 25, 26, 27, 28, 33) and the remaining were case–control studies. The studies reported outcomes for CS injections in six cases (24, 25, 26, 27, 28, 33), for HA in one case (32) and for CS or HA in the remaining four papers. The sample sizes were variable in the included studies, varying from 40 to 168 537 cases. There was no uniformity in diagnostic criteria adopted for the PJI diagnosis, and in several studies, the definition of PJI was not reported at all (25, 26, 29, 31, 33, 34). The follow-up in the studies is variable, spanning from 3 months to 71 months. The time intercurred between the last articular injection and the elective surgery is, similarly, widely variable, ranging from 2 weeks to a maximum of 42.9 months.

The quality analyses of the included studies reported the following Newcastle–Ottawa score: 8 points for five

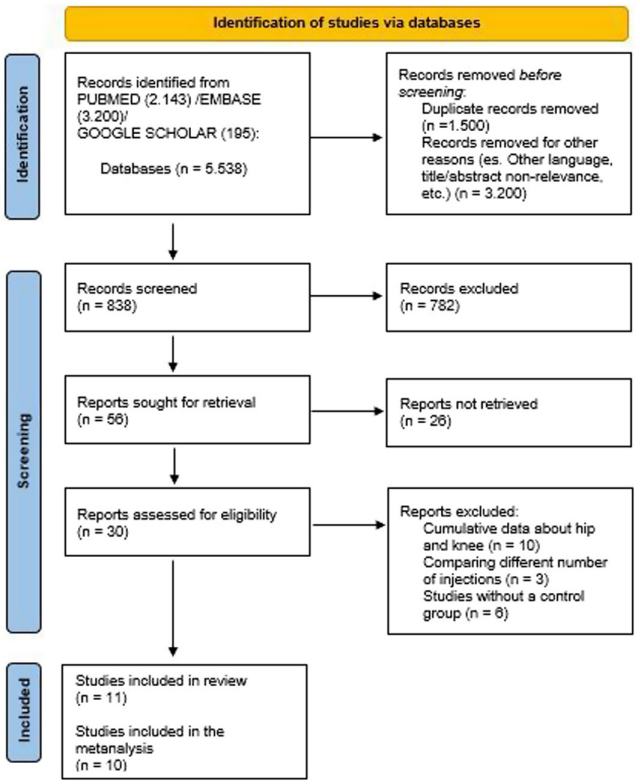


**Figure 1**
Study flowchart.

studies (24, 27, 29, 30, 33); 7 points for three studies (26, 28, 34); and 6 points for three studies (25, 31, 32).

### *Meta-analysis*

This meta-analytic process combined ten studies (24, 25, 26, 27, 29, 30, 31, 32, 33, 34), including 308 810 observations and 5272 events (PJI after articular injection). The pooling of data revealed an increased risk of PJI in the injection group (RR: 1.38, 95% CI: 1.01, 2.72) that was statistically significative ($t$ = 2.36, $P$ = 0.0427). The forest plot and the l'Abbé plot for the meta-analysis including all the studies are presented in Figs. 2 and 3, respectively. The prediction interval ranged from 0.7 to 2.72, indicating that negative risk in the injection group cannot be ruled out for future studies.

### *Study heterogeneity and sensitivity analysis*

The between-study heterogeneity variance was estimated at $\tau^2 = 0.07$ (95% CI: 0.01, 5.59), with an $I^2$ value of 55% (95% CI: 8.3%, 77.9%), indicating the presence of a moderate heterogeneity. The Baujat plot presented in Fig. 4 summarizes the influence diagnostic performed on our meta-analysis. In particular, we identified two influential studies, one having a large impact of heterogeneity but a small weight on the effect size (32) and one heavily influenced both heterogeneity and pooled effect (33). A sensitivity analysis was subsequently made by excluding the two influential cases, obtaining still a significant increase in PJI RR in the injection group, although smaller than the previous results (RR: 1.2; 95% CI: 1.08, 1.35; $t = 3.87$; $P = 0.0061$). Interestingly, in the latter analysis, the heterogeneity was annulled ($\tau^2$ = 0, 95% CI: 0; 0.9; $I^2 = 0\%$, 95% CI: 0%, 67.6%; $Q = 3.81$, $df = 7$, $P = 0.8019$) (Table 2).

### *Subgroup analysis*

In the attempt to identify a 'safe time interval' between the injection and the elective surgery, we conducted a further subgroup analysis of the papers reporting data within 12 months of interval from injection to THA procedure and in which it was possible to subdivide the time interval into three subgroups: 0–3 months, 3–6 months and 6–12 months (27, 29, 30, 31, 33). No scientific paper reported data after 12 months, and in any case, it is believed that after 1 year, there can no longer be cause–effect between the two parameters. In the subgroup 0–3 months, we noted an increased risk of PJI after injection (RR: 1.64, 95% CI: 1.44, 1.86,

**Table 1** Characteristics of the included studies.

| Study | P/R | Study design | Sample size | | Drug injected | Diagnostic criteria of PJI | Time from injection to surgery | Follow-up | NOS score |
|---|---|---|---|---|---|---|---|---|---|
| | | | Study group | Control group | | | | | |
| Kaspar & de Beer (24) | R | MC | 40 | 40 | CS | Revision caused by PJI | 0.5–42.9 mo | 29.8 mo | 8 |
| McIntosh *et al.* (25) | R | MC | 224 | 224 | CS | Not reported | Mean: 112 days | 2.7 years | 6 |
| Sreekumar et al. (26) | R | MC | 68 | 136 | CS | Not reported | Median: 11 mo | 1 year | 7 |
| Meermans et al. (27) | R | MC | 175 | 175 | CS | Identified by local clinical signs | <12 mo | 71 mo | 8 |
| Croft & Rockwood (28) | R | MC | 48 | 48 | CS | Revision caused by PJI | Mean: 5.9 mo | 10.45 mo | 7 |
| Ravi *et al.* (29) | R | CC | 1691 | 35 413 | CS or HA | Not reported | < 12 mo | 2 years | 8 |
| Schairer *et al.* (30) | R | CC | 5421 | 168 537 | CS or HA | Revision caused by PJI | <12 mo | 1 year | 8 |
| Werner *et al.* (31) | R | CC | 3368 | 31 229 | CS or HA | Not reported | <12 mo | 6 mo | 6 |
| Colen *et al.* (32) | R | CC | 118 | 495 | HA | MIS definition | <6 mo | 52 mo | 6 |
| Forlenza *et al.* (33) | R | MC | 29 058 | 29 058 | CS | Not reported | <6 mo | 6 mo | 8 |
| Tang *et al.* (34) | R | CC | 342 | 2998 | CS or HA | Not reported | 12.4 ± 11 mo | 3 mo | 7 |

CC, case–control study; CS, corticosteroids; HA, hyaluronic acid; MC, matched cohort study; MIS, Musculoskeletal Infection Society; mo, months; NOS: Newcastle–Ottawa scale; P, prospective; PJI, peri-prosthetic joint infection; R, retrospective.

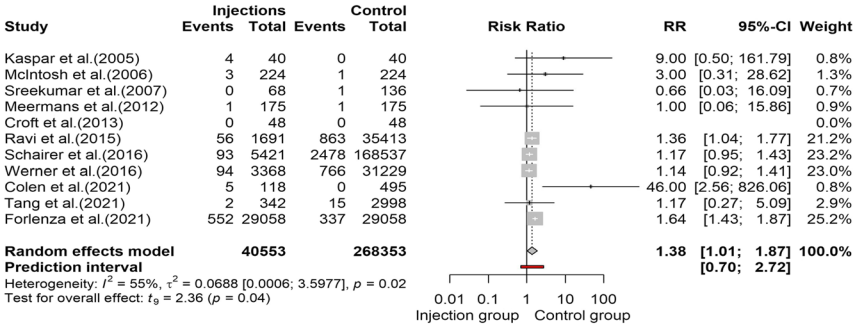


**Figure 2**
Forest plot reproducing meta-analysis of all included studies.

$P < 0.01$; $I^2 = 0\%$, $P = 0.37$). No significative increased risk was reported for the subgroup 3–6 months (RR: 1.12, 95% CI: 0.88, 1.41, $P = 0.36$; $I^2 = 56\%$, $P = 0.10$), while a significative increase in the risk of PJI after injection was identified in the <12 months group (RR: 1.20, 95% CI: 1.05, 1.36, $P < 0.01$; $I^2 = 0\%$, $P = 0.76$) (Fig. 5).

A further subgroup analysis was performed in the attempt to investigate if the type of drug injected was able to influence the overall risk of PJI. In five studies, only CS was used as a drug for injections (24, 25, 26, 27, 33). For this subgroup, the pooling of data revealed a significative increased relative risk of PJI (RR: 1.64, 95% CI: 1.44, 1.88, $P < 0.01$; $I^2 = 0\%$, $P = 0.73$). In four studies, both CS and HA were used for intra-articular injections (29, 30, 31, 34). The pooled results for this group were RR: 1.20, 95% CI: 1.05, 1.36, $P < 0.01$; $I^2 = 0\%$, $P = 0.76$. Only one study reported results for HA use only (32) (Fig. 6).

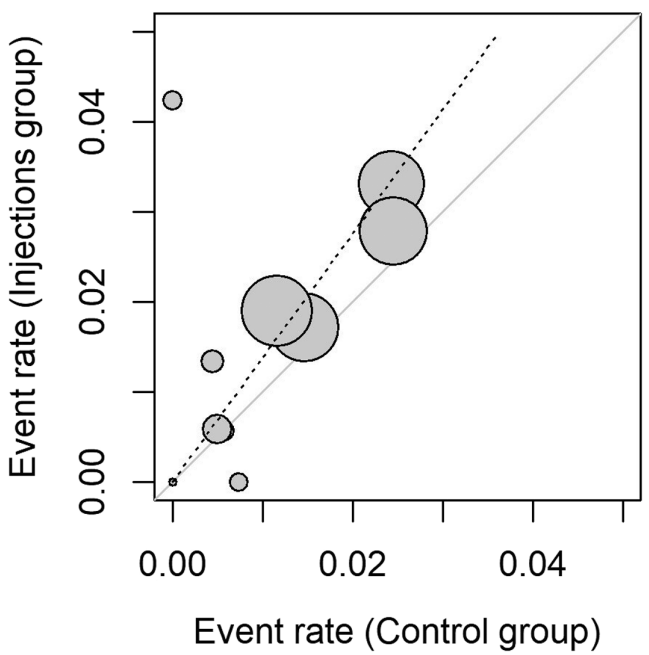


**Figure 3**
L'Abbé plot.

*Publication bias*

No publication bias was evidenced: Eggers' test does not indicate the presence of funnel plot asymmetry (intercept: 0.338; 95% CI: −0.98, −1.66; $t = 0.503$; $P = 0.63$) (Fig. 7).

## Discussion

The main finding of this meta-analysis is that intra-articular injection is a procedure that may increase the risk of developing periprosthetic infection. This risk is higher if the injection is performed less than 3 months before hip replacement.

*Hip osteoarthritis: conservative or not conservative treatments*

The demand for hip prosthetic replacement is constantly increasing. There are several well-recognized risk factors for the development of PJI, including previous invasive procedures and exposure to contaminants. PJIis one of the most serious complications of joint replacement surgery and all the most important precautions to avoid it must be implemented. A meta-analysis estimates the rate of surgical site infection to be 2.5% and the rate of deep PJI to be 0.9% after THA (35).

Patients who undergo hip replacement have often suffered from hip OA for years and have certainly resorted

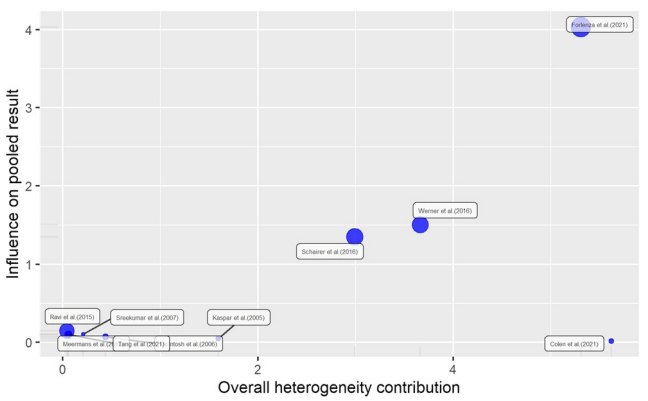


**Figure 4**
The Baujat plot for all studies.

**Table 2** Sensitivity analysis with the exclusion of the influential studies.

| Analysis | RR | 95% CI | *P* value | 95% PI | $I^2$ | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|
| Main analysis | 1.38 | 1.01–1.87 | 0.0427 | 0.70–2.72 | 55% | 8.3–77.9% | 0.018 |
| Influential cases removed* | 1.20 | 1.08–1.35 | 0.0061 | 1.03–1.41 | 0% | 0–67.6% | 0.8019 |

*Removed as influential studies and outliers: Forlenza *et al.* (33); Colen *et al.* (32). 95% PI: 95% prediction interval.

to alternative therapies before surgical treatment, and among these there are intra-articular injections.

Recently, having undergone infiltrative treatments before surgery, it has been recognized as an important risk factor for the development of PJI (33).

### *Hip infiltrative treatment and risk of periprosthetic infection: evidences from the literature*

Our meta-analysis provided cumulative evidence from 11 studies, including 308 906 observations, demonstrating a statistically significative 38% increased risk for PJI for patients who have a prior history of intra-articular injections. Our analysis, however, was deeply influenced by two studies (32, 33) that had a great impact on heterogeneity and pooled effect. The results obtained performing the sensitivity analysis, by removing the two influential studies, appear to be more realistic, providing a 20% of increased risk of PJI after intra-articular injection (RR: 1.20; 95% CI: 1.08, 1.35; $t=3.87$; $P=0.0061$) Table 2. Although reduced, the latter pooled risk is still statistically significant and in line with more recent meta-analyses (Nie *et al.* reported an RR of 1.24; 95% CI: 1.11–1.38; $P=0.002$ (36); Albanese *et al.* reported an OR=1.17; 95% CI: 1.01, 1.36; $P=0.04$ (37)).

Recently, several authors have suggested that the timing of injections before surgery could significantly influence the risk of developing PJI (33, 38), but at the moment there are no guidelines on the correct timing between hip injection and prosthetic replacement and few data are reported in the literature, as recently highlighted by Li H. *et al.* (39). Available data arise from retrospective studies which are often underpowered, with widely disparate results (25, 40). On the other hand, the conclusion of all studies is that the risk increases the shorter the time interval between intra-articular injection and THA. Therefore, one of the purposes of this meta-analysis is to clarify the minimum time that must elapse between the last hip injection and the prosthetic replacement, so as to minimize the risk of PJI. Our analysis of the pooled data demonstrated that within 3 months from injections, the risk of developing PJI appears to be 64% increased (RR: 1.64; 95% CI: 1.44, 1.86; $P < 0.01$; $I^2=0\%$; $P=0.37$). No definitive results were found for the interval time 6–12 months, in which the pooled effect had not reached the statistical significance ($P=0.36$). At 12 months, the RR returned to be in line with the general risk found for the cohort of patients who received articular injections at any time (RR: 1.20; 95% CI: 1.05, 1.36; $P < 0.01$; $I^2=0\%$; $P=0.76$). This result needs to be carefully considered in

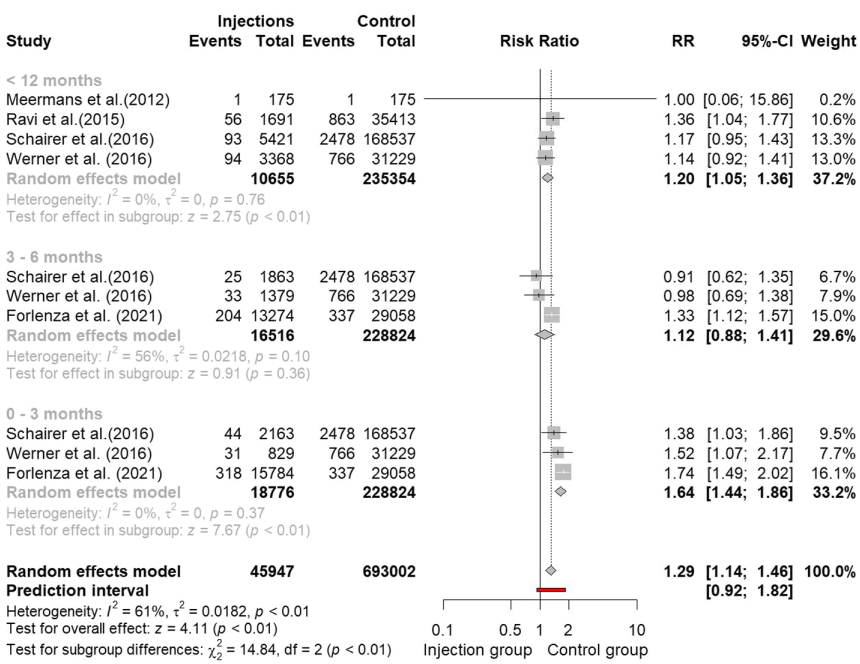


**Figure 5**
Forest plot of subgroup analysis based on timing of injection before surgery.

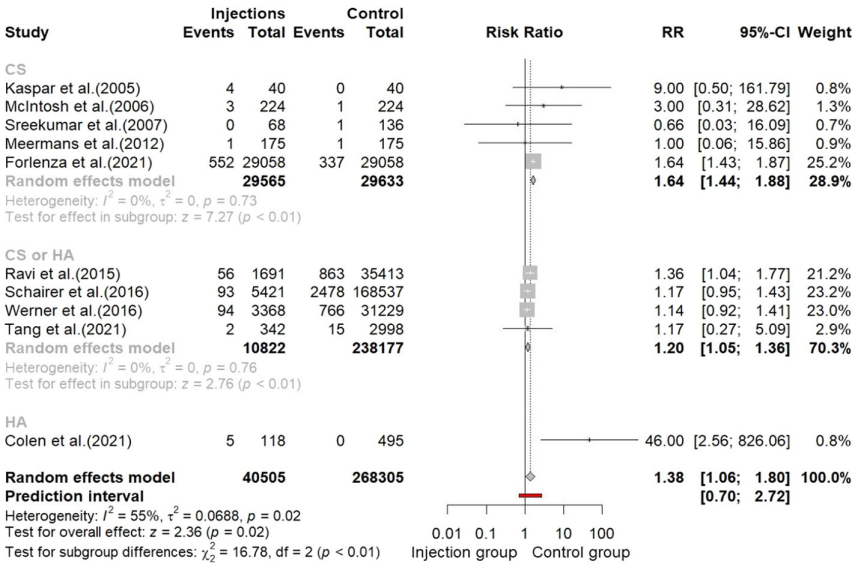


**Figure 6**
Forest plot of subgroup analysis based on type of injection.

order to reduce the risk of PJI. Although the number of available studies is still too small to accurately define the real extent of the risk, a minimum interval of 3 months is advisable between the two procedures. Albanese *et al.* confirm the same result limited to the use of CS in their recently published meta-analysis (37).

### *The role of corticosteroids*

One of the suggested pathogenetic mechanisms in developing PJI after intra-articular injections is the prolonged immunosuppressive effect of CS agents (38). In order to investigate whether the use of CS actually increases the infectious risk compared to HA, we performed a subgroup analysis based on the type of drug used for the articular injection. The available data, however, was limited. Only six studies clearly differentiated the cohort of patient who received the cohort on the basis of the drug used, in five cases CS was used (24, 25, 26, 27, 33) and in only one study HA was used (32)). Four studies did not discriminate between CS and HA (29, 30, 31, 34). None of the included studies reported results for PRP or bone marrow-derived mesenchymal stem cells (BMDC). Although the available studies did not allow to draw definitive conclusions, we found that CS articular injection significantly increases the risk of PJI with respect to the general risk (64% vs 38%). Further investigations, including other agents like PRP or BMDC, are needed, and this could be the subject of a subsequent literature review.

Similarly, it would be interesting to evaluate whether and how repeated hip injections lead to a higher risk of infection than a single one. The study by Chambers *et al.* suggests that repeated injections are associated with a statistically higher risk of infection (41).

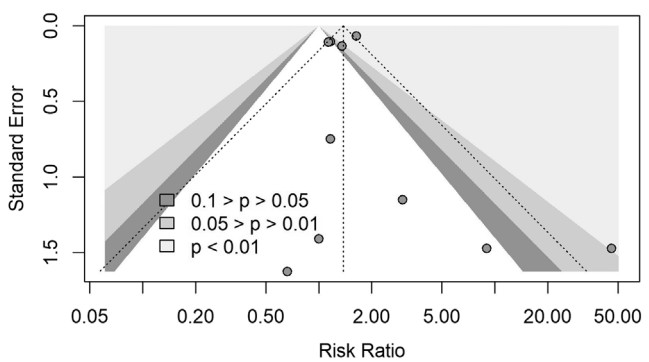


**Figure 7**
Funnel plot for identification of publication bias.

### *Limits of our meta-analysis*

Our meta-analysis has several limitations. The included studies are all retrospective, and there is heterogeneity, albeit moderate. Furthermore, almost all the studies included have foreseen the use of CS. We cannot definitively demonstrate whether this could have influenced the results. Finally, not all studies included used the Musculo Skeletal infection Society (MSIS) criteria for the diagnosis of PJI. On the other hand, there are many strengths of this meta-analysis: a high number of patients including big datasets by national registries, low publication bias and a high-quality score of the studies according to NOS.

## Conclusions

Intra-articular injection is a procedure that may increase the risk of developing PJI if performed less than 3 months before THA. For this reason, it is essential that the orthopaedic surgeon investigates whether the patient has been injected in the previous 3 months before scheduling surgery. The patient that requests infiltrative treatment of

the hip joint must be informed of this risk as well as of all possible complications.

**Supplementary materials**
This is linked to the online version of the paper at https://doi.org/10.1530/EOR-23-0028.

**ICMJE conflict of interest statement**
Luigi Zagra is an associate editor on the editorial board of EFORT Open Reviews. Luigi Zagra was not involved in the review or editorial process for this paper on which he is listed as an author. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported..

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**Author contribution statement**
MS, VC and FD collected and analysed data; GS, LZ and GL revised the manuscript.

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