Int J Clin Exp Med 2016;9(6):11002-11008
www.ijcem.com /ISSN:1940-5901/IJCEM0025053

Original Article

Intra-articular steroid injections and risk of infection following total hip replacement or total knee replacement: a meta-analysis of cohort studies

Fan-Tao Meng[1*], Bin-Bin Gong[2*], Gang Yang[1], Ying-Ze Zhang[1], Wen-Yuan Ding[1], Yong Shen[1]

[1]*Department of Orthopedics, The Third Hospital of Hebei Medical University, 139 Ziqiang Road, Shijiazhuang 050051, Hebei, People's Republic of China;* [2]*Department of Cardiology, The Second Hospital of Hebei Medical University, Shijiazhuang 050051, Hebei, People's Republic of China.* [*]*Equal contributors.*

Received January 27, 2016; Accepted April 21, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Purpose: The impact of intra-articular steroid injections on risk of infection following total hip or total knee replacement remains unclear. We conducted a meta-analysis of cohort studies to access the infection risk in patient with and without previous intra-articular steroid injections. Methods: We conducted a meta-analysis of cohort studies based on Pubmed, Embase, and Cochrane databases updated to November 2015 to access the infection risk in patient with and without previous intra-articular steroid injections. A sensitivity analysis was performed to access the stability of the pooled results. Moreover, to investigate the possible source of heterogeneity on the overall risk estimate, we performed meta-regression analyses and subgroup analyses based on sample size, surgery location, and continent. Results: Eleven studies were included in this present meta-analysis. The result of meta-analysis shows that intra-articular steroid injections were associated with the joint arthroplasty infection rate (RR, 1.436; 95% CI, 1.085-1.900), with high heterogeneity among the studies (I^2 = 53.5%; P = 0.022). Conclusion: Our findings revealed that intra-articular steroid injections may increase the joint arthroplasty infection rate. However, the result should be interpreted with caution because of the potential bias and confounding in the included studies.

Keywords: Replacement, intra-articular, steroid, injections, infection

Introduction

The infection following total hip or total knee replacement is a serious complication, often resulting in further surgery. Many factors have been approved to increase the incidence of infection, such as diabetes mellitus, obesity, nutritional deficiency, immunodeficiency, and so on [1-5]. In clinical practice, the infection following total hip or total knee replacement is frequently seen in patients with intra-articular steroid injection. It is possible that intra-articular steroid injection is another risk factor for infection after total hip or total knee replacement. However, the data looking at the association between intra-articular steroid injections and risk of infection after total hip or total knee replacement were controversial. Some studies [6-8] suggested that the widely used of intra-articular steroid injections increased the rate of infection in patients with total hip or total knee replacement, but other studies [9-12] gave a controversial conclusion. And the sample size of some studies was limitation [6, 13]. We therefore carried out this meta-analysis of cohort studies to evaluate the relationship between intra-articular steroid injections and risk of infection after total hip or total knee replacement.

Materials and methods

Search strategy and inclusion criteria

We undertook this meta-analysis according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement. A comprehensive literature search limited to English language was conducted using Pubmed, Embase, and Cochrane databases updated to November 2015. The following format of search terms was applied: ("replacement" or "replacements" or "arthroplasty") and ("inject" or "injection") and

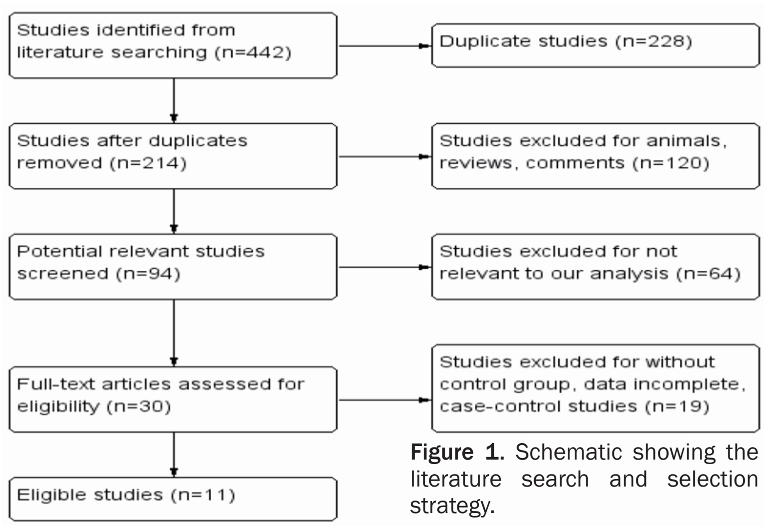

Figure 1. Schematic showing the literature search and selection strategy.

("infect" or "infection" or "infective"). Moreover, all references lists of selected articles were also manually checked to determine whether any additional articles could be included in this meta-analysis.

Articles were considered included in this study if they met the following criteria: (a) study population: adult patients with total knee replacement or total hip replacement; (b) comparison intervention: with and without intra-articular steroid injection; (c) outcome measure: the rates of infection after replacement; (d) study design: cohort study. When the same population was reported in several publications, only the most informative or complete study was included to avoid duplication of information.

Data extraction

Data were extracted from studies (when available) included first author, publication year, study design, location of surgery, interval time between injection and replacement, sample size, duration of follow-up, population characteristics, and the number of infection in each group. We contacted the authors of included studies for further information when it was necessary.

Quality assessment

The Newcastle-Ottawa Scale (NOS) [14] was applied for assessing the quality of the included studies. This tool places emphasis on the following three areas when defining the quality of observation cohort studies: the selection of the study groups (0-4 points), the comparability of the groups (0-2 points) and the determination of either the exposure or the outcome of interest (0-3 points), with a perfect score of 9.

The study selection, data extraction and quality assessment were carried out independently by two investigators (F.-T.M. and B.-B.G.). Any disagreements were resolved through discussion and consensus.

Statistical analysis

We extracted the risk ratios (RRs) of infection as the principal measure from each study. Summary risk ratios with 95% confidence intervals (CIs) were pooled across studies for this meta-analysis, and $P < 0.05$ was judged as a significant difference. Chi-square test and I^2 were used to test the heterogeneity between the studies. When a significant Chi-square test ($P < 0.10$) or $I^2 > 50\%$ indicated heterogeneity across studies, a random effects model was conducted for meta-analysis, otherwise, a fixed-effects model was conducted. Moreover, a sensitivity analysis was performed by sequential omission of individual studies in order to examine the stability of the pooled results. To investigate the possible origin of heterogeneity on the overall risk estimate, we further carried out meta-regression analyses and subgroup analyses based on sample size (≤ 10000 and > 10000), surgery location (knee or hip), and continent (North America or West Europe). Potential publication bias was detected using Begg's funnel plots and Egger's test with $P < 0.05$ judged as statistically significant.

All statistical analyses were performed using STATA, version 12.0 (StataCorp, College Station, TX). Zero total event studies1 (studies with zero infections in both injected and non-injected groups) were excluded from meta-analysis as previously recommended [15, 16].

Results

Articles selection

We retrieved 442 studies through a comprehensive literature search from PubMed,

Table 1. Characteristics of the included cohort study for meta-analysis

First author	Publication year	Country	Study type	NOS score	Surgery site	Sample size	Provider	Follow-up	DBIS
Kaspar [13]	2005	Canada	Retrospectively	7	Hip	80	Radiologist	32.8 months	NR
Papavasilou	2005	UK	Retrospectively	6	knee	144	NR	1 year	NR
McIntosh [8]	2006	USA	Retrospectively	6	hip	448	Radiologist	NR	112 days
Sreekumar [9]	2007	UK	Retrospectively	7	hip	204	NR	25-33 months	14 months
Desai [10]	2009	UK	Retrospectively	8	knee	270	NR	1-6 years	NR
Haughton [17]	2010	UK	Retrospectively	4	hip	1317	NR	NR	NR
Meermans [19]	2012	Belgium	Retrospectively	8	hip	350	Surgeon	71 months	155 days
Scroft [18]	2013	Canada	Retrospectively	7	hip	96	surgeon	10.45 months	5.9 months
Ravi [20]	2014	Canada	Retrospectively	6	hip	37881	Radiologist	2 years	0-5 years
Cancienne [7]	2015	USA	Retrospectively	7	Knee	35890	NR	6 months	0-12 months
Amin [11]	2015	USA	Retrospectively	6	knee	1628	surgeons, rheumatologists, primary care physicians	NR	0-12 months

DBIS = Duration between injection and surgery; NA = not report; UK = United Kingdom.

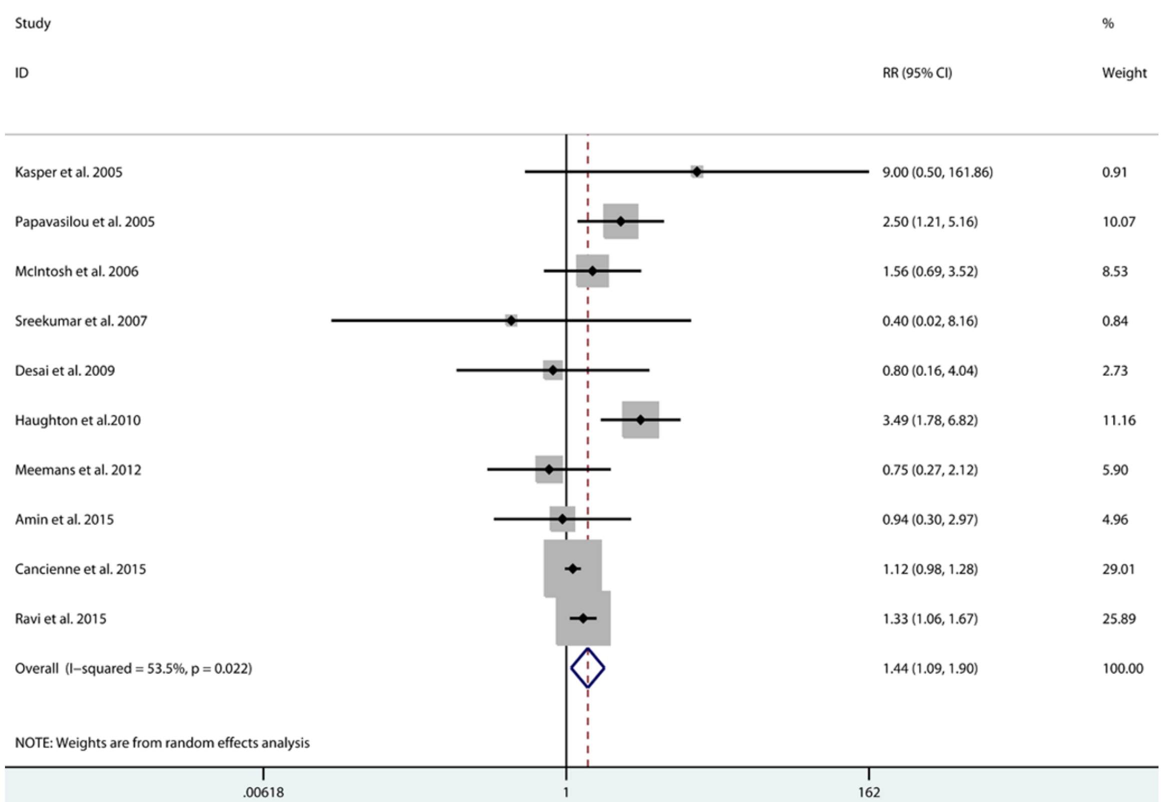

Figure 2. The results of the present meta-analysis.

EMBASE, and Cochrane databases, of which 431 studies were excluded for various reasons (duplication, reviews, comment, not human, not relevant to our analysis, without a control group, incomplete data, or case-control study) according to the title/abstract and full text (**Figure 1**). Finally, the remaining 11 cohort studies [6-11, 13, 17-20] were included in this analysis.

Study characteristics and methodological quality assessment

The main characteristics of these included cohort studies are shown in **Table 1**. These included studies were published from 2005 to 2015. The mean of the NOS score was 6.55 (ranged from 4 to 8). Two studies [10, 19] got 8 NOS scale, 4 studies [7, 9, 13, 18]

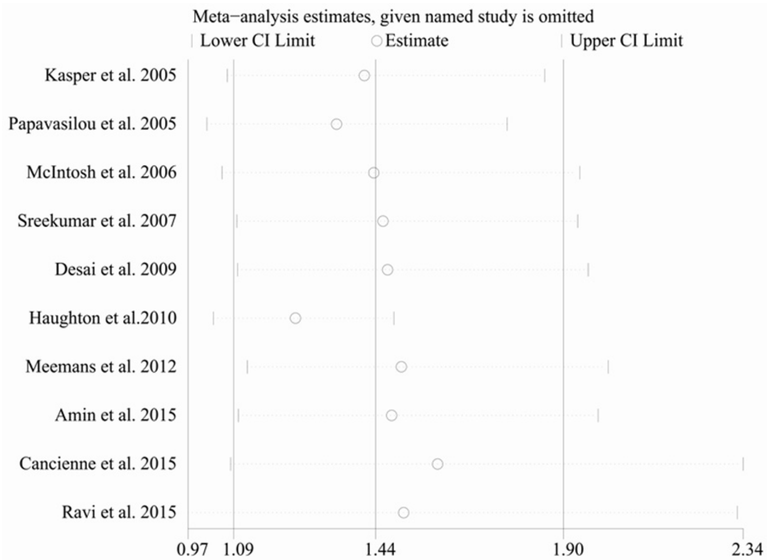

Figure 3. The results of sensitivity analyses.

got 7, 4 studies [6, 8, 11, 20] got 6, and 1 study 17 got 4. Overall, 77885 patients were enrolled in the current study. Among them, 26021 patients were conducted intra-articular steroid injection before total joint replacement.

Previous steroid injections and risk of infection following total hip or total knee replacement

The result of this meta-analysis using a random effect model was shown in **Figure 2**. Compared with the control group, there was a significant increased rate of infection among the patients with previous steroid injection (RR 1.436; 95% CI 1.085-1.900), with high heterogeneity between the studies (I^2 = 53.5%; P = 0.022). **Figure 3** shows the results of sensitivity analysis. As we sequentially omitted one study, the overall pooled RR ranged from 1.238 (95% CI, 1.035-1.481) to 1.59 (95% CI, 1.08-2.34). When we excluded the study by Haughton [17], the heterogeneity was lowest (I^2 = 17.9%; P = 0.283). Furthermore, we conducted meta-regression analyses and subgroup analyses to explain the heterogeneity based on sample size (≤ 10000 and > 10000), surgery location (knee or hip), and continent (North America or West Europe) (**Table 2**). However, the results of meta-regression analyses indicated that none of the 3 factors had significant association with the heterogeneity (all P > 0.05). Although the subgroup analyses on the 3 factors were performed, the heterogeneity of subgroups was still high.

Publication bias

There was no potential publication bias existed among the included studies tested by Begg's funnel plots (**Figure 4**) and Egger's test (P = 0.313).

Discussion

The infection following total hip or knee replacement occurs in only a small number of patients but can result in functional decline and substantial morbidity [21, 22]. Some studies [6-8] suggested that previous intra-articular steroid injection may increase the incidence of infection in arthroplasty patients. However, to the best of our known, the data regarding this topic remains inconsistent. Thus, we conducted the present meta-analysis to access the association between previous intra-articular steroid injections and infection following total hip or knee replacement.

The result of this meta-analysis indicated that intra-articular steroid injections may predispose patients to the infection following total hip or knee replacement. However, there was high heterogeneity between the studies. To explain the heterogeneity, we performed sensitivity analysis by excluding one study in each turn and the pooled RRs changed essentially. When the study by Haughton [17] was excluded, the heterogeneity was lowest (I^2 = 17.9%; P = 0.283). We found that this study got 4 NOS scale, whereas the other included studies got more than 5 NOS scale, which means that the study by Haughton [17] was low quality and should be excluded from this meta-analysis. Subsequently, meta-regression analyses and subgroup analyses based on sample size (≤ 10000 and > 10000), surgery location (knee or hip), and continent (North America or West Europe) were carried out in attempt to investigate the heterogeneity. The results of meta-regression analyses suggested that the 3 factors had no significant association with the heterogeneity (all P > 0.05) and the heterogeneity of subgroups was still high when the subgroup analyses were performed. Thus, the pooled

Table 2. Results of meta-regression analyses and subgroup meta-analyses

Subgroup	No. of studies	No. of patients	RR (95% CI)	*P*	Meta-regression	Chi-square	I^2 (%)	*P* (Heterogeneity)
Overall effect	10	77789	1.436 (1.085-1.900)	0.011		19.37	53.50	0.022
Sample size					0.21			
< 10000	8	4018	1.780 (1.265-2.504)	0.001		11.74	40.40	0.109
> 10000	2	73771	1.165 (1.037- 1.308)	0.01		1.69	40.80	0.194
continent					0.114			
North America	5	75504	1.176 (1.050-1.318)	0.005		4.19	4.60	0.381
West Europe	5	2285	1.655 (0.802-3.414)	0.173		8.89	55.00	0.064
surgery location					0.587			
Knee	4	37509	1.138 (0.998-1.297)	0.054		4.88	38.50	0.181
Hip	6	40280	1.614 (0.960-2.715)	0.071		10.94	54.30	0.053

RR = Risk ratio; CI = Confidence Interval.

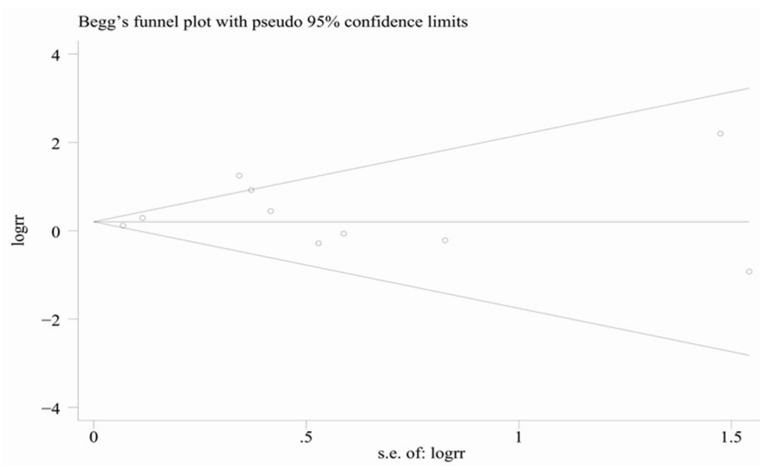

Figure 4. Begg's funnel plots showing that no potential publication bias existed.

result from this meta-analysis should be interpreted with caution due to the heterogeneity.

Although previous intra-articular steroid injections may increase the joint arthroplasty infection rate, the mechanism remains unclear. One explanation was that the steroid failed to fully dissolve leading to local immunosupression following joint arthroplasty [6, 13]. Alternatively, the infection could also be introduced through an injection, as the sterility precautions taken are often variable [23]. Some previous meta-analyses [16, 24-26] demonstrated no significant relationship between previous steroid injections and infection following total hip or knee replacement. However, those meta-analyses included small sample size studies had a limited number of patients, compared to this current meta-analysis. As the incidence of infection following total hip or knee replacement is very low [21, 22, 27], it is possible that studies with small number of patients failed to demonstrate such relationship due to low statistical power.

The findings of the present study are of clinical value to some extent. Intra-articular steroid injections of the joints have been an acceptable treatment modality to osteoarthritis patients for approximately 50 years [28]. However, the present study indicated that previous intra-articular steroid injection was a risk factor associated with joint arthroplasty infection. Thus, surgeons regarding on total hip or knee arthroplasty patients should pay more attention to the individuals with previous intra-articular steroid injections. Additionally, to reduce the incidence of infection following total hip or knee replacement, some effective measures must be taken in perioperative period.

There are several limitations in our meta-analysis. First, the low infection incidence demands large sample studies to access the significant association between intra-articular steroid injections and joint arthroplasty infection. However, some of the included studies have small sample size, which may contribute to the overestimate or underestimate of the true result. Second, the criteria for infection, dosage of injection, duration from injection to surgery, age of surgery, duration of follow up, and population country were varied among the included cohort studies. These factors may also have an influence on the joint arthroplasty infection rate. Third, certainly, this present meta-analysis can be clouded by the considerable heterogeneity among the studies.

Conclusion

Despite various limitations of the present meta-analysis, our results suggest that previous intra-articular steroid injections may increase the infection rate following total hip or knee replacement. The patients with previous intra-articular steroid injection should be given more attention to reduce the infection rate. In addition, further large-scale, well-designed RCTs on this topic are still needed.

Disclosure of conflict of interest

None.

Address correspondence to: Yong Shen, Department of Orthopedics, The Third Hospital of Hebei Medical University, 139 Ziqiang Road, Shijiazhuang 050051, Hebei, People's Republic of China. Tel: 86-031188602016; Fax: 86 031188602316; E-mail: longtaoaoyun@163.com

References

[1] Rodriguez-Merchan EC. Review article: Risk factors of infection following total knee arthroplasty. J Orthop Surg (Hong Kong) 2012; 20: 236-8.

[2] Webb BG, Lichtman DM, Wagner RA. Risk factors in total joint arthroplasty: comparison of infection rates in patients with different socioeconomic backgrounds. Orthopedics 2008; 31: 445.

[3] Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. J Hosp Infect 2015; 89: 82-9.

[4] Senthi S, Munro JT, Pitto RP. Infection in total hip replacement: meta-analysis. Int Orthop 2011; 35: 253-60.

[5] Peersman G, Laskin R, Davis J, Peterson M. Infection in total knee replacement: a retrospective review of 6489 total knee replacements. Clin Orthop Relat Res 2001; 15-23.

[6] Papavasiliou AV, Isaac DL, Marimuthu R, Skyrme A, Armitage A. Infection in knee replacements after previous injection of intra-articular steroid. J Bone Joint Surg Br 2006; 88: 321-3.

[7] Cancienne JM, Werner BC, Luetkemeyer LM, Browne JA. Does Timing of Previous Intra-Articular Steroid Injection Affect the Post-Operative Rate of Infection in Total Knee Arthroplasty. J Arthroplasty 2015; 30: 1879-82.

[8] McIntosh AL, Hanssen AD, Wenger DE, Osmon DR. Recent intraarticular steroid injection may increase infection rates in primary THA. Clin Orthop Relat Res 2006; 451: 50-4.

[9] Sreekumar R, Venkiteswaran R, Raut V. Infection in primary hip arthroplasty after previous steroid infiltration. Int Orthop 2007; 31: 125-8.

[10] Desai A, Ramankutty S, Board T, Raut V. Does intraarticular steroid infiltration increase the rate of infection in subsequent total knee replacements. Knee 2009; 16: 262-4.

[11] Amin NH, Omiyi D, Kuczynski B, Cushner FD, Scuderi GR. The Risk of a Deep Infection Associated With Intraarticular Injections Before a Total Knee Arthroplasty. J Arthroplasty 2016; 31: 240-4.

[12] Joshy S, Thomas B, Gogi N, Modi A, Singh BK. Effect of intra-articular steroids on deep infections following total knee arthroplasty. Int Orthop 2006; 30: 91-3.

[13] Kaspar S, de V de Beer J. Infection in hip arthroplasty after previous injection of steroid. J Bone Joint Surg Br 2005; 87: 454-7.

[14] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-5.

[15] Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004; 23: 1351-75.

[16] Charalambous CP, Prodromidis AD, Kwaees TA. Do intra-articular steroid injections increase infection rates in subsequent arthroplasty? A systematic review and meta-analysis of comparative studies. J Arthroplasty 2014; 29: 2175-80.

[17] Haughton D, Davey C, Sapherson D, Sefton G. Is hip injection safe and effective: The patients perspective. Rheumatology (Oxford) 2010; 49: 64.

[18] Croft S, Rockwood P. Risk of intraarticular steroid injection before total hip arthroplasty. Curr Orthop Pract 2013; 24: 185-8.

[19] Meermans G, Corten K, Simon JP. Is the infection rate in primary THA increased after steroid

injection. Clin Orthop Relat Res 2012; 470: 3213-9.

[20] Ravi B, Escott BG, Wasserstein D, Croxford R, Hollands S, Paterson JM, Kreder HJ, Hawker GA. Intraarticular hip injection and early revision surgery following total hip arthroplasty: a retrospective cohort study. Arthritis Rheumatol 2015; 67: 162-8.

[21] Salvati EA, Robinson RP, Zeno SM, Koslin BL, Brause BD, Wilson PD Jr. Infection rates after 3175 total hip and total knee replacements performed with and without a horizontal unidirectional filtered air-flow system. J Bone Joint Surg Am 1982; 64: 525-35.

[22] Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. J Bone Joint Surg Am 1999; 81: 1434-45.

[23] Charalambous CP, Tryfonidis M, Sadiq S, Hirst P, Paul A. Septic arthritis following intra-articular steroid injection of the knee--a survey of current practice regarding antiseptic technique used during intra-articular steroid injection of the knee. Clin Rheumatol 2003; 22: 386-90.

[24] Wang Q, Jiang X, Tian W. Does previous intra-articular steroid injection increase the risk of joint infection following total hip arthroplasty or total knee arthroplasty? A meta-analysis. Med Sci Monit 2014; 20: 1878-83.

[25] McMahon SE, LeRoux JA, Smith TO, Hing CB. Total joint arthroplasty following intra-articular steroid injection: a literature review. Acta Orthop Belg 2013; 79: 672-9.

[26] Marsland D, Mumith A, Barlow IW. Systematic review: the safety of intra-articular corticosteroid injection prior to total knee arthroplasty. Knee 2014; 21: 6-11.

[27] Asaid R, Williams I, Hyde D, Tiang T. Infection rates following hip and knee joint arthroplasty: large referral centre versus a small elective-only hospital. Eur J Orthop Surg Traumatol 2013; 23: 165-8.

[28] Menkes CJ. Intraarticular treatment of osteoarthritis and guidelines to its assessment. J Rheumatol Suppl 1994; 41: 74-6.