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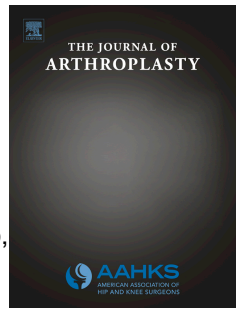

Bilateral Total Hip Arthroplasty: One-stage or Two-stage? A Meta-analysis

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Bilateral Total Hip Arthroplasty: Simultaneous or Staged? A Meta-Analysis

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Bilateral Total Hip Arthroplasty: One-stage or Two-stage?

A Meta-analysis

Abstract

Introduction: Total hip arthroplasty (THA) is one of the most successful orthopaedic surgeries performed in the last 50 years. However, controversies still exist between conducting one-stage or two-stage bilateral THA.

Materials and Methods: Using Pubmed, Ovid, Embase and Cocharane library databases, we searched for papers written between January 1995 and October 2015 that contained the following search terms: “one-stage or two-stage” or “simultaneous or staged”, and “hip” and “arthroplasty or replacement”. A meta-analysis was conducted with the collected pooled data about major and minor systemic complications, surgical complications and other perioperative data associated with one-stage and two-stage bilateral THA. Statistical analysis was performed by the Mantel-Haenzel method, and the fixed effect model was used to analyze data.

Results: There were 13 studies with 17,762 patients who underwent one-stage bilateral THA and 46,147 patients who underwent two-stage bilateral THA. One-stage bilateral THA had a lower risk of major systemic complications, less deep venous thrombosis (DVT), and shorter operative time compared to two-stage bilateral THA. There were no significant differences in death, pulmonary embolism (PE), cardiovascular complication, infections, minor complications, and other surgical complications between procedures.

Conclusion: One-stage bilateral THA was superior to two-stage in terms of major systemic complication, DVT and surgical time compared to two-stage bilateral THA. However, this study does not encourage performing one-stage over two-stage bilateral THA. Higher evidence level studies are necessary for further analysis.

Introduction

Total hip arthroplasty (THA) is one of the most successful orthopaedic surgeries performed during the last 50 years, as patients have reported high satisfaction and improved activities of daily living[1]. Most patients that undergo THA suffer from primary osteoarthritis, and previous studies have demonstrated that patients who undergo unilateral THA may require a contralateral procedure within 10 years[2,3]. Conditions such as avascular necrosis, rheumatoid arthritis, ankylosing spondylitis, and developmental dysplasia can affect both hips and may potentially require bilateral THA surgery. However, just because both hips are affected does not necessarily indicate that bilateral THA surgery needs to be performed.

After Charnley et al[4] first reported performing one-stage (simultaneous) bilateral THA in 1971, many papers focused on one-stage bilateral THA[5-7]. However, controversies still exist regarding one-stage or two-stage (staged) bilateral THA. The benefits of one-stage bilateral THA include patients only undergo anesthesia once and have only one hospital stay, which means shorter overall hospital length of stay (LOS)[8,9] and cost reduction[10]. Some studies advocate one-stage bilateral THA, as they have demonstrated that the rates of perioperative complications are similar between one-stage bilateral THA and unilateral THA[7,11]. On the other hand, other opposing studies have found that one-stage bilateral THA pose greater risks to patients, with increased transfusions, greater adverse events, and suboptimal functional outcomes[12,13].

In 2008, Tsiridis et al[14] did a previous systemic review and meta-analysis of one-stage versus two-stage bilateral THA. They only compared thromboembolic complications and dislocation rates with the pooled data, since other parameters had significant heterogeneity, and they found that there were no significant differences between procedures. In 2010, Haverkamp et al[15] also conducted a meta-analysis comparing one-stage versus two-stage bilateral THA, but their meta-analysis only included 5 studies. Additionally, both meta-analyses lacked precision, as both of them took unilateral THA patients, then doubled this patient population when they underwent a second THA to count as two-stage bilateral THA patients. This is compared to true two-stage bilateral THA patients, who had planned THA at a

set time interval. Additionally, these studies were conducted greater than 5 years ago. Since then, researchers have introduced new surgical techniques and clinical protocols[16-19]. Thus, there is a need for an updated meta-analysis comparing one-stage versus two-stage bilateral THA to include more recent studies and a greater number of outcomes.

Therefore, the purpose of this study was to conduct a meta-analysis comparing the differences between one-stage and two-stage bilateral THA in terms of mortality, pulmonary embolism (PE), deep venous thrombosis (DVT), cardiovascular complications and systemic or surgical complications, including infection, as well as, operative time, blood loss, and transfusion rate.

Materials and Methods

A systemic review and meta-analysis was performed using the method described by the Cochrane Handbook[20] and reported with the PRISMA[21] checklist guidelines.

Search Strategy

Using Pubmed, Ovid, Embase and Cocharane library databases, studies were searched between January 1995 and October 2015 that contained the following search terms: “one-stage or two-stage” or “simultaneous or staged”, and “hip” and “arthroplasty or replacement.” The bibliographies of any relevant review and meta-analysis were also checked for potentially eligible papers.

Eligibility Criteria

In order to be included in this study, the papers reviewed had to meet the following criteria: (1) patients had to undergo primary THA; (2) studies that compared one-stage bilateral versus two-stage bilateral THA; and (3) reported results including any parameters of surgical time, blood loss, transfusion, cost, hospital LOS, death, PE, DVT, cardiovascular complication, pulmonary complication, any other systemic or surgical complications. We excluded any studies comparing bilateral to unilateral THA, studies that evaluated other hip replacement surgeries, such as resurfacing or revision THA, and studies that assumed that unilateral THA performed twice were two-stage bilateral THA.

Study selection and data extraction

Two orthopaedics surgeons independently screened studies by titles and abstracts to ensure that they met the eligibility criteria. Subsequently, the full text of each potential suitable study was reviewed. If there was disagreement between the reviewers, a third orthopedic surgeon was consulted to determine if the study should be included.

Once the final studies were determined that met the criteria, we extracted the study design, the number of study subjects, demographic data (age and gender), and time of publication. Corresponding authors of each of the studies were contacted to ask for additional and missing data, but no additional information was obtained.

For determining the outcomes investigated in this meta-analysis, we examined parameters that were evaluated when deciding to do a one- or two-stage bilateral THA. The decision of which procedure to perform is often based on the number of possible complications. Thus, our primary objective was to compare major adverse complications between one-stage and two-stage bilateral THA. Major complications were defined as death, PE, DVT, cardiovascular complications, pulmonary complications, gastric ulcers, gastric bleeding and neurological complications. These major complications were also separately analyzed between the two procedures. The second objective was to compare minor systemic complications, surgical complications and surgical related parameters between the two groups. Minor complications were defined as all digestive complications except gastric ulcers or bleeding, postoperative urinary complications, anemia and other systemic complications not included in major complications. We divided surgical complications into infection and other surgical complications besides infection, since infection correlates with prolonged surgical time [22]. We also compared surgical time, blood loss, transfusion rate, cost and hospital LOS.

Study quality

Since prospective randomized control trials, prospective cohort studies and retrospective observational studies were all included, we used Cochrane Collaboration's tool[20] for prospective, randomized studies and the Newcastle-Ottawa quality scale[23] for prospective cohort studies and retrospective observational studies to assess the risk of bias. The

Newcastle-Ottawa Scale, which was used for non-randomized studies included in this meta-analysis, is a quality assessment tool where 9 indicates the highest quality study based on 3 categories (selection, comparability and exposure/outcome). Two orthopaedic surgeon reviewers assessed the quality of eligible studies independently, and if there was disagreement, it was discussed with a third orthopaedic surgeon.

Statistical analysis

RevMan (Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012) was used to perform statistics, and $p<0.05$ was set as statistically significant. We calculated the mean difference (MD) for continuous data and odds ratio (OR) for dichotomous data with 95% confidence interval (CI) for each outcome. For studies that reported continuous variables with ranges instead of standard deviation (SD), we use the Walter's method[24] to estimate SD with range data. The meta-analysis was performed by the Mantel-Haenzel method, and the fixed effect model was used to analyze the data. We used χ^2 and I^2 to test the heterogeneity. I^2=0% indicates low heterogeneity, while I^2=100% indicates high heterogeneity. If $\chi^2<0.1$ or $I^2>50\%$, then the studies were interpreted as heterogeneous and the random-effects model was re-applied to complete the meta-analysis. Publication bias was assessed by funnel plots, which is a scatter plot of treatment effect versus an assessment of study error, where there was lower bias if all publications fell within a symmetric funnel, and higher bias if publications fell outside of the symmetric funnel.

Results

Study selection and characteristics

There were 689 relevant studies from our initial database search. After evaluating the titles and abstracts, there were 27 full-text articles. Among these studies, 14 were excluded, leaving 13 studies for the meta-analysis. **Figure 1** demonstrates the study selection flow.

Among these thirteen studies, 1 was a prospective, randomized study, 1 was a prospective cohort study, 7 were retrospective observational studies, and 4 reported on registry or national

data (**Table 1**). All studies involved 63,909 patients, of which 17,762 patients underwent one-stage bilateral THA and 46,147 patients underwent two-stage bilateral THA.

Methodological Quality of Included Studies

Table 2 summarizes the quality assessment of studies. One study was a randomized control trial (RTC) with random sequence, allocation concealment and blinding assessment. Among the other twelve non-randomized studies, the studies had scores ranging from 5 to 7 using the Newcastle-Ottawa Scale quality assessment. The score for selection, comparability and exposure/outcome were 4, 2, and 2, respectively, and the qualities of these studies were acceptable.

Complications

Major systemic postoperative complications were less in one-stage bilateral THA compared to two-stage bilateral THA based on 11 studies (OR = 0.53; 95% CI 0.36–0.77; p = 0.001; heterogeneity: Chi^2=15.68, I^2= 36%, **Figure 2**), but there was no statistical difference between the two groups with regards to cardiovascular complications (OR = 0.81; 95% CI 0.40–1.64; p = 0.56; heterogeneity: Chi^2=4.32, I^2= 0%, **Table 3**). Four studies (59,480 patients) provided data on postoperative death related to surgery. Of the 16,676 patients that underwent one-stage THA, 21 patients died in 90 days after surgery, the mortality rate was 0.13%. And of the 42,804 two-stage THA patients, 127 patients died in 90 days after surgery, the mortality rate was 0.3%. There was no statistically significant difference of mortality between the two groups (OR = 0.75; 95% CI 0.38-1.49; p = 0.41; heterogeneity: Chi^2= 4.25, I^2= 29%).

With regards to thromboembolic events, there were seven studies that evaluated PE (3,775 patients) and DVT (4,259 patients). There were no differences between one-stage and two-stage bilateral THA groups for developing PE (OR = 1.08; 95% CI 0.47–2.48; p = 0.86; heterogeneity: Chi^2= 2.74, I^2= 0%, **Figure 3**), but one-stage bilateral THA patients were less

likely to develop a DVT compared to two-stage bilateral THA patients (OR = 0.37; 95% CI 0.16–0.85; p = 0.02; heterogeneity: Chi^2= 5.59, I^2= 0%, **Figure 4**).

There were 6 studies that provided data on minor systemic complications, but there were no significant differences between one-stage and two-stage groups (OR = 1.22; 95% CI 0.61-2.46; p = 0.57; heterogeneity: Chi^2= 20.38, I^2= 75%, **Table 3**). There were 4 studies that provided data on infectious complications (including deep and superficial infection), and the pooled data showed a statistically higher infection rate in one-stage versus two-stage bilateral THA (OR = 2.17; 95% CI 1.27-3.71; p = 0.004; heterogeneity: Chi^2= 3.50, I^2= 14%). Of the 13 total studies, 8 studies evaluated other surgical complications except infection, and the pooled data showed no significant difference between the one-stage and two-stage groups (OR = 1.18; 95% CI 0.87-1.61; p = 0.28; heterogeneity: Chi^2= 9.86, I^2= 29%). The cumulative operative time was shorter in one-stage than two-stage bilateral THA groups (MD = -7.30; 95% CI -13.18-1.41; $p<0.05$, heterogeneity: Chi^2= 5.65, I^2=47%). With regards to blood loss and allogeneic transfusions (4 studies), there were no significant differences between the one-stage and two-stage bilateral THA groups (blood loss: MD = 42.75; 95% CI -277.65-363.15; p = 0.79; heterogeneity: Chi^2= 58.82, I^2= 95%, allogeneic transfusions: MD = 0.17; 95% CI -0.98-1.33; p = 0.77; heterogeneity: Chi^2= 203.20, I^2= 99%), but the heterogeneity of minor systemic complications, blood loss and transfusion studies were high (I^2=75, 95 and 99%, respectively) and should be interpreted carefully.

Publication bias

The funnel plot of studies for major systemic complication indicates mild asymmetry, suggesting moderate evidence of publication bias (**Figure 5**).

Discussion

Ever since Charnley first implemented one-stage bilateral THA, many studies have been conducted to address the controversial risks and benefits of one-stage bilateral THA compared to two-stage bilateral THA. especially about complications and higher transfusion rates.

Previous systematic reviews and meta-analysis[14,15] studies had small numbers of two-stage bilateral THA studies included and do not include more recent studies. Thus, the purpose of our study was to compare one-stage to two-stage bilateral THA with regards to major and minor complications.

Our pooled data indicated that two-stage bilateral THA group had more major complications than the one-stage bilateral THA group. The report from Aghayev et al[17], which included 1819 patients, indicated that two-stage bilateral THA patients have a higher rate of major systemic complications. Most studies indicate that one-stage bilateral THA patients are often younger and have less preoperative comorbidities, but theoretically, patients that undergo two-stage bilateral THAs experience approximately twice the risk of a single procedure[10,16,29]. Previous reports showed no difference in systemic complication between one-stage bilateral THA and unilateral THA[7, 30]. If major systemic complications accumulate with each successive surgery, then it seems reasonable that the complication rate is higher for two-stage bilateral THA patients.

Within major complications, the mortality rate from the four pooled studies was not different between groups. Our mortality rates were little less than other studies, which have estimated that the mortality rate is 0.3% and 0.65% following the first 30 and 90 days, respectively, after primary THA[31]. Recently published data using a national database with more than a half million cases reported that the inpatient primary THA mortality rate was 0.13%[32]. Older patients undergoing THA have a higher mortality rate postoperatively compared to younger patients[33,34]. Cardiovascular complications and pulmonary embolism are the most common reasons that THA patients die postoperatively[35], but our data demonstrated no difference in cardiovascular complications and pulmonary embolism between one-stage and two-stage bilateral THA. Although the two-stage bilateral THA patients were older and possibly had higher comorbidities, one-stage patients had longer surgical time and more blood loss. This could justify the lack of statistical difference in mortality rate between both groups.

The risk of DVT did differ between groups. During a prolonged surgical procedure, increased blood loss can induce Virchow's triad and result in venous thromboembolism (VTE)[36]. However, some reports have showed no difference in the incidence of VTE between one-stage bilateral THA and unilateral THA[25,37], as Babis et al[38] combined five studies and found that the one-stage bilateral THA group had a lower DVT incidence than unilateral THA group, with no difference in the number of PE. Similar to our study, Tsiridis et al combined three studies and found no difference between one-stage and two-stage bilateral THA with regard to VTE [14]. However, Tsiridis et al did not separate DVT from PE, and this posed some limitations. When we separated out the patient cohorts, we determined that there were greater DVT in two-stage bilateral THA but no difference in PE. The higher DVT rate in the two-stage bilateral THA group may have resulted from the following: 1) the two-stage bilateral THA group underwent two procedures while one-stage group only underwent one; and 2) two-stage THA patients may have limited rehabilitation ability after the first surgery because of pain in their contralateral hip. DVT and PE may have different results, as previous studies have shown that PE and DVT may be unrelated[39,40].

In our study, we found no statistical difference in minor systemic complications such as postoperative anemia and urinary problems. However, Alfaro-Adrian et al[9] reported more minor complications in the two-stage bilateral THA group, whereas Parvizi et al[8] and Eggli et al[25] reported more minor complications in one-stage bilateral THA patients. The other three included studies reported no difference between these two groups[17,18,26].

On the other hand, complications like infection were higher in the one-stage bilateral THA group compared to the two-stage group. Due to the limitations in the studies included in the meta-analysis, we grouped PJI and superficial surgical infections (SSI) cases together. SSI increase the duration of a patient's hospital stay and may lead to periprosthetic joint infection (PJI)[22]. One-stage bilateral THA cases have longer surgical times (for one procedure), but lower operative time cumulatively. Pulido et al[41] reported that increased operative time and allogenic blood transfusion are predisposing factors for PJI, as allogenic transfusions can

transmit infectious agents and modulate the immune system to increase the risk of infection[42]. While the results of our study showed that there were no differences in blood loss and transfusion between these two groups, other studies have demonstrated different findings[9,26]. Surgical technique, hemostasis, tranexamic acid, transfusion criteria and the use of blood saving devices can influence blood loss and transfusion, which possibly explains the variations in our results.

Additionally, there were no differences in other surgical complications such as neuropraxia, dislocation or intraoperative fracture. A previous meta-analysis also showed no difference in dislocation between one-stage and two-stage bilateral THA [14], and the majority of these complications arose due to surgical technique and not the difference between one- and two-stage bilateral THA.

There were four studies that compared operative time between one-stage and two-stage bilateral THA, and our results demonstrated that it took less surgical time to complete one-stage bilateral THA than the two-stage procedure. However, surgical time varies depending on the surgical approach, patient's position and surgeon experience. With the direct anterior approach, surgeons can begin the second procedure while closing the wound from the first procedure[43]. One-stage surgery limits the patient's exposure to anesthesia to only one occasion. Although we could not include this data in the meta-analysis, all evaluated studies that reported LOS and cost indicated a shorter stay and lower cost in the one-stage group compared to the two-stage bilateral THA. We found the same results as in the previous systemic review [14].

Though thirteen studies were pooled and the meta-analysis was conducted, there were still some limitations in our analysis. First, we combined prospective and retrospective studies with registry data, as an ideal meta-analysis would only contain prospective RCTs. However, when the data was analyzed with the Mantel-Haenzel method, most of the results were found to be homogeneous. Second, we did not subgroup two-stage bilateral THA patients based on the time interval between each stage, and different interval times may have resulted in different

outcomes. We attempted to subgroup studies by interval time of two-stage bilateral THA, but due to the variability of interval times and that only 5 studies reported interval times, we could not consolidate two-stage bilateral THAs at certain time points. Third, most of the studies included did not mention surgical approach, patient position, and diagnostic criteria of complications or transfusion criteria. Fourth, there was limited demographic data, and most demographic variables such as comorbidities could not be compared using a meta-analysis. Last, there was moderate evidence of publication bias and some of the parameters had high heterogeneity. However we used random effect model with if it had high heterogeneity. All of these pose a potential bias risk for the meta-analysis, but these factors could not be regulated since they were not provided.

In summary, if patients have bilateral hip disease, one-stage bilateral THA has less major complications, DVTs and decreased operative time, costs and shorter hospital lengths of stay, but increased infections compared to two-stage bilateral THA. However, this study does not encourage performing one-stage over two-stage bilateral THA. Since there are risks and benefits to both procedures, these potential complications must be interpreted in light of each individual patient's needs and concerns. Further studies are needed to provide higher quality of evidence to evaluate the two procedures.

Reference

1. Harris WH. The First 50 Years of Total Hip Arthroplasty. Clin Orthop Relat Res 2009:467:28–31.

2. Sayeed SA, Johnson AJ, Jaffe DE, et al. Incidence of Contralateral THA After Index THA for Osteoarthritis. Clin Orthop Relat Res 2012:470:535–540.

3. Goker B, Block JA. Risk of contralateral avascular necrosis (AVN) after total hip arthroplasty (THA) for non-traumatic AVN. Rheumatol Int 2006;26:215–219.

4. Jaffe WL, Charnley J. Bilateral Charnley low-friction arthroplasty as a single operative procedure: a report of fifty cases. Bull Hosp Jt Dis 1971;32(2):198-214.

5. Kim YH. Bilateral Cemented and Cementless Total Hip Arthroplasty. J Arthroplasty. 2002;17(4):434-40.

6. Schafer M, Elke R, Young JR, et al. Safety of one-stage bilateral hip and knee arthroplasties under regional anaesthesia and routine anaesthetic monitoring J Bone Joint Surg Br 2005;87B:1134-1139.

7. Stavrakis AI, SooHoo NF, Lieberman JR. Bilateral Total Hip Arthroplasty has Similar Complication Rates to Unilateral Total Hip Arthroplasty. J Arthroplasty 2015;30:1211-1214.

8. Parvizi J, David T, Sheikh E, et al. Bilateral total hip arthroplasty One-stage versus Two-stage procedures Clin Orthop Relat Res 2006;453:137–141.

9. Alfaro-Adrian J, Bayona F, Rech JA, et al. One- or Two-stage bilateral total hip replacement. J Arthroplasty 1999;14(4):439-445.

10. Reuben JD, Meyers SJ, Cox DD, et al. Cost comparison between bilateral simultaneous, staged and unilateral total joint arthroplasty. J Arthroplasty 1998;13(2):172-179.

11. Kim YH, Kwon OR, Kim JS. Is one-stage bilateral sequential total hip replacement as safe as unilateral total hip replacement? J Bone Joint Surg Br 2009;91B:316-20.

12. Berend KR, Lombardi AV, Adams JB. Simultaneous vs Staged Cementless Bilateral Total Hip Arthroplasty Perioperative Risk Comparison. J Arthroplasty 2007;22(6):111-115.

13. Ritter MA, Stringer EA. Bilateral total hip arthroplasty: a single procedure. Clin Orthop Relat Res 1980;149:185–190.

14. Tsiridis E, Pavlou G, Charity J, et al. The safety and efficacy of bilateral simultaneous total hip replacement an analysis of 2063 cases. J Bone Joint Surg Br 2008;90B:1005-12.

15. Haverkamp D, Bekerom M, Harmse I, et al. One stage bilateral total hip arthroplasty, is it safe? A meta-analysis. Hip Int 2010;20(4):440-448.

16. Hooper Gj, Hopper NM, Rothwell AG, et al. Bilateral total joint arthroplasty The early results from the New Zealand National Joint Registry. J Arthroplasty 2009;24(8):1174-1177.

17. Aghayev E, Beck A, Staub LP, et al. Simultaneous bilateral hip replacement reveals superior outcome and fewer complications than two-stage procedures: a prospective study including 1819 patients and 5801 follow-ups from a total joint replacement registry. BMC Musculoskeletal Disorders 2010;11:245-254.

18. Lindberg-Larsen M, Joergensen CC, Husted H, et al. Simultaneous and staged bilateral total hip arthroplasty: a Danish nationwide study. Arch Orthop Trauma Surg 2013;133:1601–1605.

19. Garland A, Rolfson O, Garellick G, et al. Early postoperative mortality after simultaneous or staged bilateral primary total hip arthroplasty: an observational register study from the swedish hip arthroplasty register. BMC Musculoskeletal Disorders 2015;16:77-85.

20. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

21. Moher D, Liberati A, Tetzlaff J, et al. Methods of systematic reviews and meta-analysis Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Journal of Clinical Epidemiology 2009;62:1006-1012.

22. Zhu Y, Zhang F, Chen W, et al. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. Journal of Hospital Infection 2015;89:82-89.

23. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in Meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

24. Walter SD, Yao X. Effect sizes can be calculated for studies reporting ranges for outcome variables in systematic reviews. Journal of Clinical Epidemiology 2007;60:849-852.

25. Eggli S, Huckell CB, Ganz R. Bilateral total hip arthroplasty One stage versus Two stage procedures Clin Orthop Relat Res 1996;328:108–18.

26. Bhan S, Pankaj A, Malhotra, R, et al. One- or two-stage bilateral total hip arthroplasty a prospective, randomized controlled study in an Asian population. *J* Bone Joint Surg Br 2006;88B:298-303.

27. Saito S, Tokuhashi Y, Ishii T, et al. One- versus Two-stage bilateral total hip arthroplasty. Orthopedics 2010;33(8):453-458.

28. Linda RJ, Benedict AC, Rami JA, et al. Bilateral simultaneous hip replacement versus bilateral sequential hip replacement A 7-year data review. Orthopaedic Nursing 2011;30:119-123.

29. Rasouli MR, Maltenfort MG, Ross D, et al. Perioperative Morbidity and Mortality Following Bilateral Total Hip Arthroplasty. J Arthroplasty 2014;29:142-148.

30. Parvizi J, Pour AE, Peak L, et al. One-stage bilateral total hip arthroplasty compared with unilateral total hip arthroplasty. J Arthroplasty 2006;21(6):26-31.

31. Berstock JR, Beswick AD, Lenguerrand E, et al. Mortality after total hip replacement surgery A systematic review. Bone Joint Res 2014;3:175-182.

32. Illingworth KD, El Bitar YF, Banerjee Devraj, et al. Inpatient mortality after primary total hip arthroplasty: Analysis from the national inpatient sample database. J Arthroplasty 2015;30:369-373.

33. Singh JA, Lewallen DG. Ninety-day mortality in patients undergoing elective total hip or total knee arthroplasty. J Arthroplasty 2012;27(8):1417-1422

34. Lie SA, Pratt N, Ryan P, et al. Duration of the increase in early postoperative mortality after elective hip and knee replacement. J Bone Joint Surg Am. 2010;92:58-63.

35. Ashley Blom, Giles Pattison, Sarah Whitehouse, et al. Early death following primary total hip arthroplasty: 1727 procedures with mechanical thrombo-prophylaxis. Acta Orthopaedica 2006;77(3):347-350.

36. Macaulay W, Salvati EA, Sculco TP, et al. Single-stage bilateral total hip arthroplasty. J American Academy of Orthopaedic Surgeons 2002;10(3):217-221.

37. Burak Beksac, Alejandro Gonzalez Della Valle, John Anderson, et al Symptomatic thromboembolism after one-stage bilateral THA with a multimodal prophylaxis protocol. Clin Orthop Relat Res 2007;463:114-119.

38. Babis GC, Sakellariou VI, Johnson EO, et al. Incidence and prevention of thromboembolic events in one stage bilateral total hip arthroplasty: A systematic review current vascular pharmacology. 2011;9:24-32.

39. Parvizi J, Jacovides CL, Bican O, et al. Is deep vein thrombosis a good proxy for pulmonary embolus? J Arthroplasty 2010;25(6):138-144.

380 40. Westrich GH, Farrell C, Bono JV, et al. The incidence of venous thromboembolism after
381 total hip arthroplasty. J Arthroplasty 1999;14(4):456-463.

382 41. Pulido L, Ghanem E, Joshi A, et al. Periprosthetic joint infection The incidence, Timing,
383 and Predisposing Factors. Clin Orthop Relat Res 2008;466:1710–1715.

384 42. Raghavan M, Marik PE. Anemia, Allogenic blood transfusion, and immunomodulation in
385 the critically ill. Chest 2005;127(1):295-307.

386 43. Shih CH, HoWB. One-stage versus two-stage bilateral autophor cetamic total hip
387 arthroplasty. Clin Orthop Relat Res 1985;193:141-5.

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Table 1: Characteristics of the selected studies.

Author (year)	Study type	Country	One-stage Bilateral THA			Two-stage Bilateral THA		
			n	Sex (M/F)	Age (years)	n	Sex (M/F)	Age (years)
(1996) Eggli[26]	Prospective cohort	Switzerland	64	26/38	54	191	108/83	61.3
(1998) Reuben[10]	Retrospective cohort	USA	7	4/3	49	8	1/7	57
(1999) Alfaro-Adrian[9]	Retrospective cohort	UK	95	40/55	65	107	42/65	63.9
(2006) Bhan[25]	Randomized control trial	India	83	54/29	46.6	85	51/34	43.4
(2006) Parvizi[8]	Retrospective case control	USA	98	53/45	53	98	46/52	65
(2007) Berend[12]	Retrospective cohort	USA	167	100/67	52.7	110	47/63	57.3
(2009) Hooper[16]	Registry	New Zealand	303		61	743		61
(2010) Aghayev[17]	Retrospective cohort	Switzerland	247	116/131	59	1572	794/778	62.5
(2010) Saito[27]	Retrospective case control	Japan	49	6/43	59	40	4/36	61.9
(2011) Johnston[28]	Retrospective cohort	UK	68	26/42	61.5	526	208/318	66.5
(2013) Lindberg-Larsen[18]	Registry	Denmark	103	59/44	55.7	577	234/343	66.9
(2014) Rasouli[29]	National database	USA	14,798		58.4	1532		60.3
(2015) Garland[19]	Registry	Sweden	1,680	767/913		40558	16,356/24,202	
Total			**17,762**	**1,251/1,410**		**46147**	**17,891/25,981**	

THA=Total hip arthroplasty; n=number of patients; M=male; F=female; USA=United States of America; UK=United Kingdom.

Table 2: Quality of selected studies

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
(2006) Bhan[25]	Yes	Yes (sealed envelope)	Unclear	Yes	Yes	Unclear	Unclear

Study	Study type	Newcastle-Ottawa Scale			
		Selection	Comparability	Exposure/Outcome	Total score
(1996) Eggli[26]	Prospective cohort	3	2	2	7
(1998) Reuben[10]	Retrospective cohort	3	1	1	5
(1999) Alfaro-Adrian[9]	Retrospective cohort	3	1	2	6
(2006) Parvizi[8]	Retrospective case control	3	1	2	6
(2007) Berend[12]	Retrospective cohort	3	1	2	6
(2009) Hooper[16]	Registry	3	1	2	6
(2010) Aghayev[17]	Retrospective cohort	3	1	2	6
(2010) Saito[27]	Retrospective case control	4	1	2	7
(2011) Johnston[28]	Retrospective cohort	4	1	2	7
(2013) Lindberg-Larsen[18]	Registry	4	1	2	7
(2014) Rasouli[29]	National database	3	1	2	6
(2015) Garland[19]	Registry	3	1	2	6

Table 3: Comparison of complications (major, minor, and surgical) and other parameters between one-stage and two-stage bilateral THA.

Variables	Studies	Number of patients (One-stage/Two-stage) Bilateral THA	Overall effect		Heterogeneity	
			p-value	MD/OR (95% CI)	Chi^2	I^2 (%)
Cardiovascular complication	6	690/2630	0.56	0.81(0.40-1.64)	4.32	0
Death	4	16676/42804	0.41	0.75(0.38-1.49)	4.25	29
Minor complications	6	690/2,630	0.57	1.22 (0.61-2.46)	20.38	75
Infection	4	557/1,931	0.004*	2.17 (1.27-3.71)	3.50	14
Other surgical complication	8	876/3,208	0.28	1.18 (0.87-1.61)	9.86	29
Operative time	4	325/330	0.02*	-7.30 (-13.18 to 1.41)	5.65	47
Blood loss	4	325/330	0.79	42.75 (-277.65 to 363.15)	58.82	95
Transfusion	4	443/400	0.77	0.17 (-0.98 to 1.33)	203.20	99

THA=Total hip arthroplasty; MD=mean difference; OR=odds ratio; CI=confidence interval.
* statistically significant.

Figure Legend

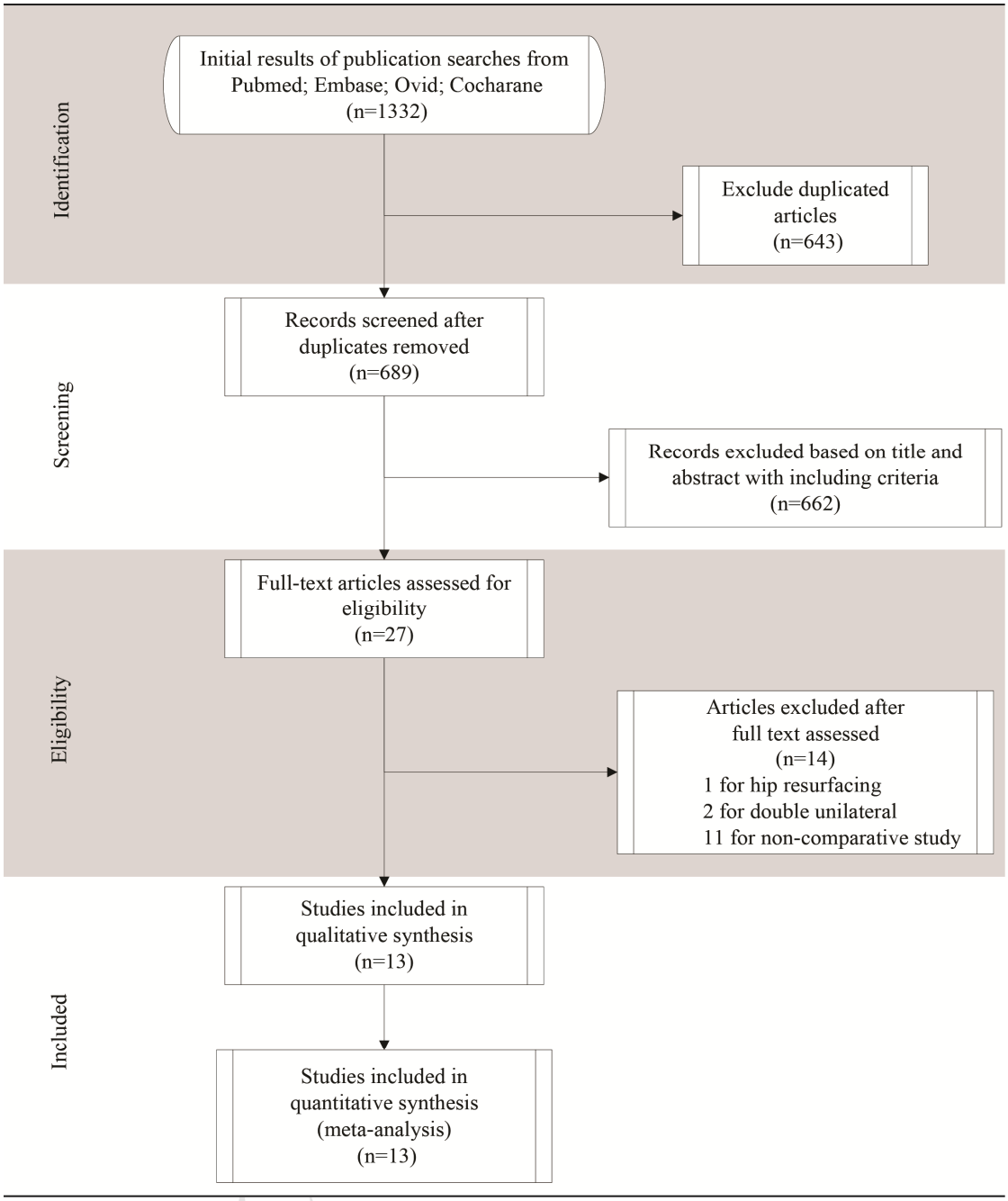
Figure 1: Flow diagram showing study selection for the meta-analysis.

Figure 2: Forest plot showing the odds ratio and 95% CI for postoperative major systemic complication.
M-H= Mantel-Haenszel; CI=Confidence interval.

Figure 3: Forest plot demonstrating the odds ratio and 95% CI for postoperative pulmonary embolism.
M-H= Mantel-Haenszel; CI=Confidence interval.

Figure 4: Forest plot demonstrating the odds ratio and 95% CI for postoperative deep vein thrombosis.
M-H= Mantel-Haenszel; CI=Confidence interval.

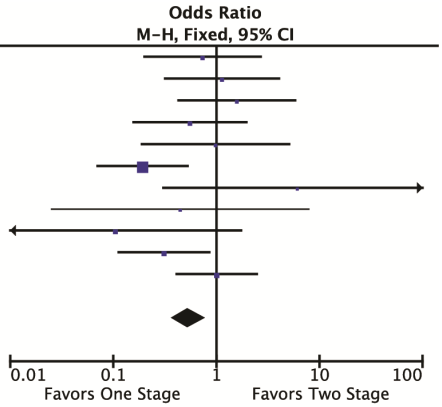
Figure 5: Funnel plot for major systemic complication, demonstrating evidence of publication bias.



Study or Subgroup	One Stage Events	One Stage Total	Two Stage Events	Two Stage Total	Weight	Odds Ratio M-H, Fixed, 95% CI
(1996) Eggli[26]	3	64	12	191	6.7%	0.73 [0.20, 2.69]
(1999) Alfaro-Adrian[9]	5	95	5	107	5.2%	1.13 [0.32, 4.04]
(2006) Bhan[25]	6	83	4	85	4.3%	1.58 [0.43, 5.81]
(2006) Parvizi[8]	4	98	7	98	7.9%	0.55 [0.16, 1.95]
(2009) Hooper[16]	2	303	5	743	3.4%	0.98 [0.19, 5.08]
(2010) Aghayev[17]	4	247	124	1572	38.8%	0.19 [0.07, 0.53]
(2010) Saito[27]	3	49	0	40	0.6%	6.10 [0.31, 121.60]
(2011) Johnston[28]	0	68	8	526	2.3%	0.45 [0.03, 7.80]
(2013) Lindberg-Larsen[18]	0	103	25	577	9.1%	0.10 [0.01, 1.73]
(2014) Rasouli[29]	15	14798	5	1532	10.6%	0.31 [0.11, 0.85]
(2015) Garland[19]	5	1680	120	40588	11.1%	1.01 [0.41, 2.47]
Total (95% CI)		**17588**		**46059**	**100.0%**	**0.53 [0.36, 0.77]**
Total events	47		315			

Heterogeneity: Chi² = 15.68, df = 10 (P = 0.11); I² = 36%

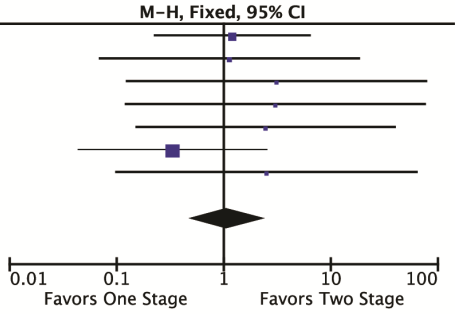
Test for overall effect: Z = 3.29 (P = 0.0010)



Study or Subgroup	One Stage Events	Total	Two Stage Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
(1996) Eggli[26]	2	64	5	191	23.0%	1.20 [0.23, 6.34]
(1999) Alfaro-Adrian[9]	1	95	1	107	8.8%	1.13 [0.07, 18.28]
(2006) Bhan[25]	1	83	0	85	4.6%	3.11 [0.12, 77.42]
(2006) Parvizi[8]	1	98	0	98	4.7%	3.03 [0.12, 75.31]
(2009) Hooper[16]	1	303	1	743	5.5%	2.46 [0.15, 39.41]
(2010) Aghayev[17]	1	247	19	1572	48.5%	0.33 [0.04, 2.49]
(2010) Saito[27]	1	49	0	40	5.0%	2.51 [0.10, 63.18]
Total (95% CI)		**939**		**2836**	**100.0%**	**1.08 [0.47, 2.48]**
Total events	8		26			

Heterogeneity: $Chi^2 = 2.74$, df = 6 (P = 0.84); $I^2 = 0\%$

Test for overall effect: Z = 0.18 (P = 0.86)



Study or Subgroup	One Stage Events	Total	Two Stage Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
(1996) Eggli[26]	0	64	3	191	7.5%	0.42 [0.02, 8.19]
(1999) Alfaro-Adrian[9]	0	95	4	107	17.9%	0.12 [0.01, 2.27]
(2006) Bhan[25]	3	83	2	85	8.1%	1.56 [0.25, 9.56]
(2009) Hooper[16]	1	303	4	743	9.8%	0.61 [0.07, 5.50]
(2010) Aghayev[17]	0	247	28	1572	33.0%	0.11 [0.01, 1.80]
(2010) Saito[27]	1	49	0	40	2.3%	2.51 [0.10, 63.18]
(2013) Lindberg-Larsen[18]	0	103	16	577	21.3%	0.16 [0.01, 2.76]
Total (95% CI)		**944**		**3315**	**100.0%**	**0.37 [0.16, 0.85]**
Total events	5		57			

Heterogeneity: $Chi^2 = 5.59$, df = 6 (P = 0.47); $I^2 = 0\%$
Test for overall effect: Z = 2.34 (P = 0.02)