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Original Article

Use of beta-blockers and risk of aseptic loosening in total hip and knee arthroplasty: a nested case – control study

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Abstract

Objectives: To analyze the effect of beta-blockers on the risk of aseptic loosening (AL) in Total Hip (THA) or Knee (TKA) Arthroplasty. **Methods:** A nested case-control study was conducted. Cases were patients who underwent revision surgery for THA or TKA due to AL. Controls were patients who sustained primary THA or TKA and were matched to cases in respect to age, sex, type of prostheses and follow-up in a 4:1 ratio. The use of beta-blockers was achieved. A logistic regression analysis adjusted to potential confounders was performed to determine the risk of AL. Analysis was also adjusted to cardioselectivity of the beta-blocker and the adherence to treatment, measured as Proportion of Days Covered (PDC). **Results:** 24 cases and 96 controls were selected. Compared to non-users, any use of beta-blockers was associated with a reduced risk of AL [adjusted OR 0.141 (Confidence Interval (CI) 95% 0.04-0.86)]. Use of selective beta-blockers showed significant lower risk of AL [adjusted OR 0.112 (CI95% 0.01-0.91)]. PDC ≥50% was associated with reduced risk of AL compared to non-users [adjusted OR 0.083 (CI95% 0.01-0.66)]. **Conclusion:** The first clinical evidence showing an association between the use of beta-blockers and lower risk of aseptic loosening in THA and TKA is provided.

Keywords: Beta-Blockers, Aseptic Loosening, Arthroplasty, Implants, Knee

Introduction

Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) are very common orthopedic procedures performed worldwide[1,2], as they can lead to a significant improvement in the in quality of life for patients with end stage arthritic conditions. In an ageing society with greater demands on mobility, the number of joint replacements is expected to increase dramatically. The American Academy of Orthopaedic Surgeons predicts that by 2030, more than 474,000 primary TKAs will be performed annually in the United States[3]. Consequently, the number of revision surgeries will also increase, causing a considerable burden on patients and health systems worldwide.

Hip and knee revision procedures are technically-demanding, associated with higher complications rates, and poorer clinical results compared with primary joint replacement. Moreover, prosthetic revision surgeries are relatively expensive, associated with an average cost around $5,000 to $10,000. In addition, these costs are projected to increase due to the continuous evolution of the implants[4,5].

Aseptic loosening is the most frequent cause of revision in both TKA and THA, representing about 35% and 55.2% of the cases respectively[6,7]. However, little is known about its etiology. Several factors have been proposed as possible causes, which can be divided into host-, genetic-, surgical- and prosthesis-related factors, although no consensus has been reached regarding the degree of influence of each one[8].

The authors have no conflicto of interest.

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The autonomous nervous system is an important regulator of bone turnover[9,10]. Several retrospective studies have reported a relation between the use of beta-adrenergic receptor antagonists and a reduction of fracture risk of about 15 to 30%[11-13]. The beta-2 adrenergic receptor blockade in bone leads to an increase in differentiation and proliferation of osteoblasts and a decrease in osteoclasts function, so it has a dual bone formation response[14-16]. On the other hand, there is strong evidence in the literature suggesting that the recruitment of osteoclast precursors and their subsequent differentiation play major roles in wear particle-induced osteolysis and aseptic loosening[17,18]. Accordingly, the administration of beta-blockers could potentially inhibit aseptic loosening through the inhibition of osteoclastic function. However, the role of beta-blockers in the development of aseptic loosening in TKA and THA has not been established. The objective of this study is to analyze the effect of beta-blockers on the risk of aseptic loosening in THA or TKA.

Materials and methods

Data source

Approval from the ethical committee of the Hospital Regional Universitario de Málaga was obtained to carry out a nested case-control study on patients with primary hip or knee arthroplasties living within the local health area of the city of Malaga. Records of patients in our healthcare area were identified in the computerized database of the Traumatology and Orthopedic Surgery Department. The guidelines of the World Medical Association Declaration of Helsinki for research involving Human Subjects were followed.

Study population

We identified patients who underwent primary THA or TKA in our hospital between January 2010 and December 2014. Data were reviewed from January 2015 to April 2016. We only included patients who underwent THA using Hardinge's transgluteal approach, and were implanted uncemented femoral and acetabular components (CORAIL/PINNACLE hip system®, DePuy Orthopaedics, Warsaw, IN, USA), and a ceramic-polyethylene bearing surface. In addition, only patients who had cruciate retaining TKA (Triathlon® total knee system, Stryker Orthopaedics, Mahwah, NJ, USA) with a cemented tibial component and an uncemented femoral component were included.

Case definition

Cases were defined as patients who required revision surgery of a primary THA or TKA due to aseptic loosening between January 2010 and December 2014.

Patients with a history of haemophilia, joint instability, prosthetic infections, allergies to prosthetic components, large malalignment deformities, peri-prosthetic fractures, femoral neck fractures, inadequate surgical technique, broken prosthetic components, incomplete clinical history and primary THA or TKA performed before 2010 were excluded. Infection was excluded by at least 2 negative cultures taken in revision surgery in all cases. In addition, patients with missing data, medical conditions that could alter bone metabolism (i.e., Paget disease, alcoholism, osteomalacia, malignant tumors excluding basal cell carcinoma), and treated with medications that could alter bone metabolism (i.e., corticosteroids, anticonvulsants, antipsychotic or anti-osteoporosis drugs) were also excluded. The follow–up time was defined as the period in months between the primary arthroplasty to the revision surgery.

Control definition

Controls included patients who did not require revision surgery. Controls were subject to the same exclusion criteria as cases. Patients were randomly matched by age (+/- 2 years), gender, prosthetic type (THA/TKA) and follow-up time (+/- 6 months) in a 4:1 ratio. Follow-up time was defined as the period in months between the joint replacement to the revision of data. All the matched controls were still alive at the end of the study period.

Exposure assessment

We ascertained the use of selective (i.e., atenaolol, bisoprolol,) and non-selective beta-blockers (i.e., propranolol, carvedilol, labetalol, and oxpronolol) at the time of the primary joint replacement in cases and controls. Patients who were never treated with beta-blockers before were considered non-users. In addition, adherence was analyzed using the Proportion of Days Covered (PDC) during the follow-up period. The PDC is defined as the proportion of time the patient is under treatment, and it is calculated as number of days taking the drug/number of days of follow-up. Patients were divided into two different categories of PDC (<0.50, and ≥0.50).

Sample size calculation

The sample size was calculated using a G* Power statistical software (Universitaat Dusseldorf, Germany). We performed a priori analysis for differences between two independent proportions. Beta error was set at 80% and alpha error at 5%. Accordingly, we estimated that the total sample size would be 119 patients.

Statistical analysis

We performed conditional logistic regression analyses using statistical analysis system SPSS Statistics version 20.0 (IBM, Armonk, NY). Crude and adjusted risk estimates were presented as odds ratios (OR) with 95% confidence intervals (CI). P values were considered statistically significant if less than 0.05.

Odds ratios for prosthetic revision surgery were adjusted

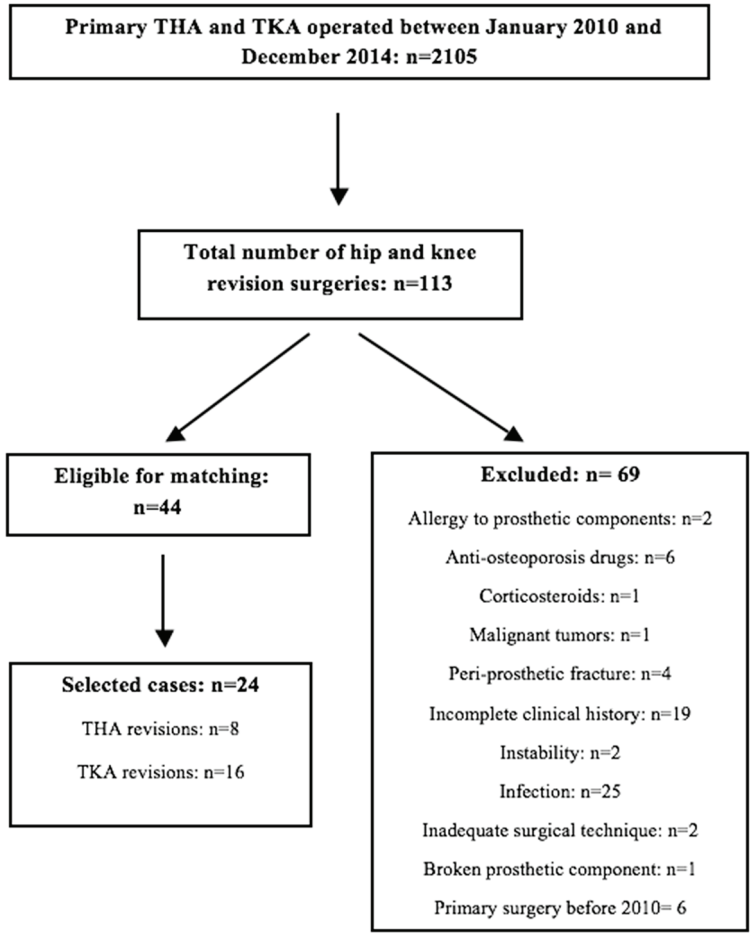

Figure 1. Flowchart describing cases selection process.

for the following potential confounders: Body Mass Index (BMI), Charlson Comorbidity Score (CCS), smoking status (none, current) and exposure to drugs that could influence the bone osseo-integration (i.e., proton pump inhibitors and selective serotonin reuptake inhibitors [SSRIs]). The distribution of the samples was analysed using the Shapiro-Wilk test. Differences between groups were assessed with Student's T Test and Mann Whitney U Test for continuous variables, and Chi Square test for nominal variables.

Results

A total of 2105 primary hip or knee replacement surgeries were performed in our center between January 2010 and December 2014. In addition, 113 THR and TKR revision surgeries were performed during the same period. Among these, 44 cases fulfilled the inclusion and exclusion criteria (14 THA revisions and 30 TKA revisions) (Figure 1). On the other hand, we reviewed the records of 740 patients who underwent primary hip or knee arthroplasty surgery during the study period and did not require revision surgery (307 THA and 433 TKA). A total of 447 primary joint replacements were considered eligible controls for matching (159 THA and 288 TKA) (Figure 2). After the matching process we concluded with 24 cases (8 THA revisions, and 16 TKA revisions) and 96 controls (32 THA and 64 TKA) (Figure 2). The demographic characteristics of both groups are shown in Table 1.

The number of cases treated with beta-blockers was 2 (8.4%), compared with 31 (31.3%) among controls (Table 2). The crude and adjusted OR (95% CI) of undergoing revision surgery compared to controls, were 0.19 (CI95%: 0.04-0.86; p=0.02) and 0.14 (CI95% 0.02-0.55; p=0.007), respectively for users of beta-blockers (Table 2). Mean PDC in cases was 37.5% (47.37) and 75.28% (25.84) in controls (p=0.16).

Patients treated with selective beta-blockers had a significantly lower risk of undergoing revision surgery compared to non-users of beta-blockers. The adjusted OR (95% CI) of undergoing revision surgery compared to controls, was 0.11 (0.01-0.91) for any use of selective beta-blockers. The use of non-selective beta-blockers, however, did not show significant differences (Table 2). When we

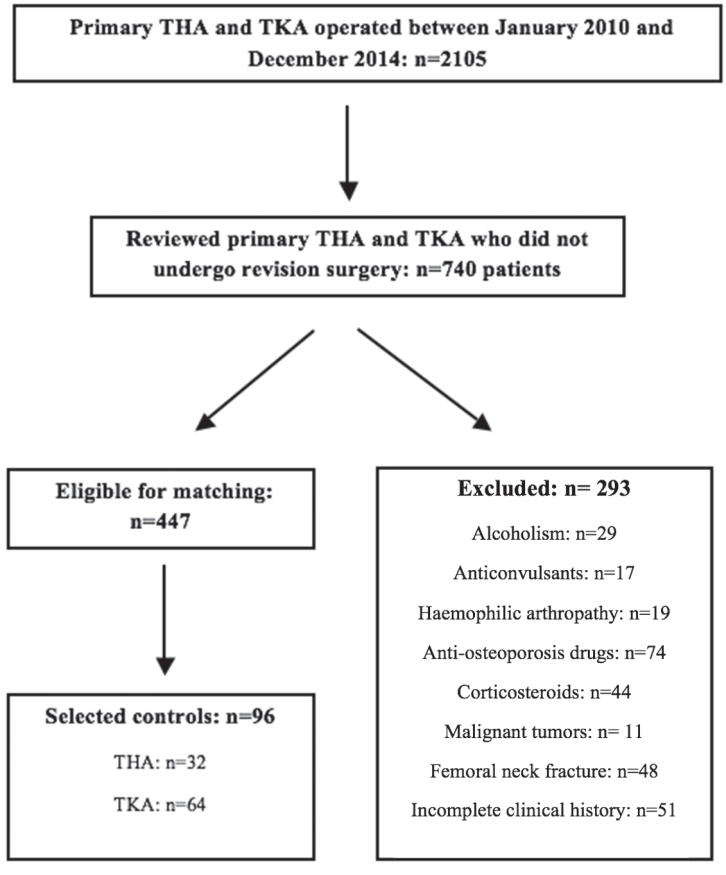

Figure 2. Flowchart describing controls selection.

Table 1. Distribution of patient characteristics in cases and controls.

Demographic features	Cases (n=24)	Controls (n=96)	p
Age‡	69.67 (8.3)	70.31 (5.67)	NS
Gender‡			
Male	8 (33.3)	32 (33.3)	NS
Female	16 (66.7)	64 (66.7)	
Side			
Right	15 (62.5)	57 (59.4)	NS
Left	9 (37.5)	39 (40.6)	
Type of Prosthesis‡			
THA	8 (33.3)	32 (33.3)	NS
TKA	16 (66.7)	64 (66.7)	NS
CCI	3.8 (1.65)	3.82 (1.24)	NS
Smokers	3 (12.5)	5 (5.2)	NS
BMI§	29.58 (4.07)	31.04 (2.74)	NS
Drugs			
Use of SSRI	2 (8.3)	11 (11.5)	NS
Use of PPI	18 (75)	56 (58)	NS
Follow up‡	30.46 (11.48)	35.8 (13.56)	NS

*Data are presented as No. (%) or mean (SD). Abbreviations: THA, Total Hip Arthroplasty; TKA, Total Knee Arthroplasty; CCI, Charlson comorbidity Index PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors; NS, Not significant. *Percentages may not sum 100% due to rounding. ‡Matching variables. §Measured as weight in kilograms divided by the square of height in meters. p values were considered statistically significant if less than 0.05.*

Table 2. Crude and adjusted odd ratios for association of revision surgery with the use of beta-blockers.

Use of BB	Cases (n= 24)	Controls (n= 96)	Crude OR	Adjusted OR¥	CI 95%
No use	22 (91.6)	65 (67.7)	1	1	Ref
Any use	2 (8.4)	31 (31.3)	0.191	0.141	(0.02-0.55)*
Selective BB ‡	1 (4.2)	19 (19.8)	0.155	0.112	(0.01-0.91)*
Non-selective BB γ	1 (4.2)	12 (12.5)	0.246	0.190	(0.02-1.58)
PDC < 0.5	1 (4.2)	4 (4.2)	0.739	0.481	(0.05-4.76)
PDC ≥ 0.5	1 (4.1)	27 (28.1)	0.109	0.083	(0.01-0.66)*

*Data are presented as No. (%). Abbreviations: OR, odd ratio; CI, confidence interval; BB, beta-blockers. ‡ Atenaolol, bisoprolol. γ Propranolol, carvedilol, labetalol, and oxpronolol. * Statistically significant: p value <0.05 ¥Adjusted for: Charlson's comorbidity index, body mass index, smoking status, use of proton pump inhibitors, and use of selective serotonin reuptake inhibitors.*

examined the adherence to treatment, the adjusted OR (95% CI) for beta-blockers-users with PDC ≥0.5 compared to non-users was 0.08 (0.01-0.66); the adjusted OR for users with PDC<0.5 compared to non-users showed no significant results (Table 2).

Discussion

In this study, we found that the use of beta-blockers was associated with a lower risk of aseptic loosening in THA and TKA. This is the first clinical study specifically designed to assess the effect of beta-blockers on the risk of aseptic loosening in patients undergoing joint replacement surgery. These findings provide further evidence on the association between the adrenergic system and the bone metabolism[19,20].

The long-term implant survival of joint replacement procedures depends on the osseointegration of the implant whether it's cemented or uncemented[21]. Osseointegration and bone healing are similar processes that involve almost the same growth factors, cells and cytokines[22]. Therefore, drugs that enhance bone healing and improve bone metabolism, such as beta-blockers, can also enhance osseointegration[19,23]. However, there are no clinical studies that have analyzed the relation between the use of beta-blockers and the risk of prosthetic revision in orthopedic surgery.

Beta-blockers and bone

The use of beta-blockers has widely shown to be related with beneficial effects on bone metabolism. There is increasing evidence demonstrating that the use of beta-blockers is associated with a reduction of the fracture risk in elderly patients[11,13,20,24,25]. In a meta-analysis that estimated the effect of antihypertensive drugs on the fracture risk, Wiens et al[26] reported that beta-blockers decreased the risk of any fracture by 14%, and the hip fracture risk by 28%. This protective effect can be partially attributed to a possible increase in bone mineral density (BMD) associated with the use of these drugs[13].

On the other hand, other studies have reported that beta-blockers do not increase bone formation markers like osteocalcin and procollagen type-I N-terminal propeptide in postmenopausal women[27]. However, the clinical implications of these reports are somehow limited, because in these studies fractures were not considered a primary outcome. Other authors have observed a higher risk of fracture in beta-blockers users compared with non-users[28]. These results were attributed to higher orthostatic hypotension and syncope rates induced by beta-blockers. A recent meta-analysis performed on several observational studies reported a statistically significant reduction in the relative risk of any fracture of 15% in patients taking beta-blockers[11].

Beta-blockers improve bone metabolism by inhibiting osteoclasts activity, enhancing osteoblastic proliferation and causing a net gain in bone turnover[19,21]. Bonnet et al[29] demonstrated that the administration of low-dose of propranolol improved bone formation and prevented osteoclasts proliferation in ovariectomized rats. Moreover, in a recent animal study, propranolol reduced bone resorption, and RANKL expression in rats, as well as IL-1β and TNF-α levels. RANKL is expressed on osteoblasts and binds to specific RANK receptors on osteoclasts. The activation of the RANK receptors on osteoclasts eventually leads to their activation; therefore, increasing local bone resorption. Tumor necrosis factor-alpha (TNF) stimulates RANKL-induced osteoclastogenesis via coupling of TNF type 1 receptor and RANK signaling pathways[30]. An increased IL-1β expression leads to osteoclast differentiation which can also increase bone resorption. Moreover, the administration of propranolol has been found to increase the expression of OPG in animal models. OPG is a natural inhibitor of RANKL receptors on osteoblasts, and its activation is associated with a decrease in bone turnover. Propranolol has also been found to suppress in vitro osteoclast differentiation and its resorptive activity by inhibiting the nuclear factor of activated T cells (NFATc)1[31].

In this study, we observed a reduction in the risk of aseptic loosening associated with the use of selective beta-blockers. Other studies have observed that the effect of selective agents on the fracture risk was inconclusive[14]. Some authors have stated that selective agents were more effective than non-selective ones in the reduction of the fracture risk[32]. However, further research is needed to clarify the influence of the cardioselectivity of the beta-blocker on bone metabolism.

Our findings also indicate that patients with higher adherence rates to beta-blockers had a lower risk of aseptic loosening. Therefore, the effect of beta-blockers on the survival of the prosthetic components seems to be dependent on the exposure time.

Aseptic loosening and drugs

Aseptic loosening is a multifactorial entity that often leads to the failure of joint replacement surgery. Several surgical, biological and mechanical strategies have been developed to reduce its incidence. Surprisingly, reports on the influence of pharmaceutical drugs on the rates of aseptic loosening or implant failure are limited.

The processes of osseointegration and fracture healing are remarkably similar and depend on the activation of growth factors and cytokines that are co-ordinated during the different phases of bone formation and remodelling[33]. Accordingly, implant insertion in bone triggers an early inflammatory response that, lastly, leads to death of the osteocytes and activation of the osteoclasts, which causes increased bone resorption around the prostheses during the first postoperative weeks[34]. Moreover, it has been well documented that bone resorption favors early implant migration and, ultimately, impairs osseointegration[17,35-37]. On the other hand, aseptic loosening is the result of a biologic reaction including particle phagocytosis, an inflammatory response phase mediated by cytokines, followed by a periprosthetic osteolytic phase mediated by cytokines, receptor activator for nuclear factor κ B Ligand (RANKL) β, and osteoprotegerin (OPG).

Strategies focused on decreasing osteoclasts activity during the early postoperative period have been proposed to decrease bone resorption after implant insertion. As an example, there is strong evidence suggesting that peri-operative treatment with bisphosphonates reduces implant early migration[38,39]. Prieto-Alhambra et al[40] found that in patients undergoing lower extremity arthroplasty, the use of bisphosphonates resulted in almost a twofold increase in implant survival. Erythromycin therapy has also been proposed as a useful tool in the prevention of aseptic loosening in joint replacement surgery as it has shown to diminish the inflammatory response secondary to the wear debris particles[41]. However, there are no reports on the clinical implications of these finding.

Our findings suggest that beta-blockers could have a protective effect against aseptic loosening following joint replacement surgery. Perhaps these drugs could be used in the future as a prophylactic treatment in patients with poor bone quality who could potentially have a higher risk of aseptic loosening.

Strengths and limitations

This nested case-control study was the first specifically designed to assess the association between aseptic loosening in joint replacement surgery and use of beta-blockers. Moreover, our analyses of odds ratios were adjusted to several confounders that may affect the results of our study including: body mass index, smoking status, Charlson's comorbidity index, and exposure to medications known to alter bone metabolism.

However, our study also presents several limitations. The observational and retrospective design of the study impedes the establishment of causality between the use of beta-blockers and the prevention of aseptic loosening in joint replacement surgery. Moreover, the sample size of the study was limited by our restrictive inclusion criteria that aimed to reduce the selection bias. In addition, the regression analysis in this study did not include other factors that could influence the aseptic loosening rates, such as physical activity, diet, and calcium levels. However, the effect of beta-blockers on the aseptic loosening rates was evident in the crude analysis, before adjusting to other potential confounders. The strict inclusion and exclusion criteria, the matching process and the adjusted logistic regression analyses ensure the comparability of groups. Furthermore, due to its design, this epidemiological study cannot determine if the lower rates of aseptic loosening associated with the use of beta-blockers, is attributed to their positive effect on BMD, to their influence on the pathways involved in bone healing, or to a combination of both factors. Finally, future randomized controlled trials designs will be needed to confirm the results of this study.

Conclusions

This study provides the first clinical evidence showing an association between the use of beta-blockers and a lower risk of aseptic loosening of total hip and total knee arthroplasties. Patients with low adherence did not benefit from this effect. The selectivity of the beta-blockers influences the aseptic loosening rates.

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