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Proton Pump Inhibitors and the Risk of Early Aseptic Loosening in Hip and Knee Arthroplasty

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Abstract

Introduction: The use of proton pump inhibitors (PPIs) has been associated with a higher risk of osteoporotic fractures and non-unions rates. However, the relation between the use of PPIs and the development of aseptic loosening in arthroplasty procedures has not been studied. The objective of this study is to analyze the relation between the use of PPIs, and the risk of early aseptic loosening in total knee arthroplasty (TKA) and total hip arthroplasty (THA). **Materials and methods:** A nested case-control study was conducted on patients who were subjected THA or TKA in our center between 2010 and 2014. Cases were patients subjected to revision surgery due to early aseptic loosening during the study period. Cases were matched with controls who did not require any type of revision surgery by type of joint replacement (THA/TKA), gender, age (+/− 2 years), and follow-up time (±6 months). Odds Ratios were adjusted to potential confounders. **Results:** The crude and adjusted ORs (95% CI) of undergoing revision surgery for aseptic loosening following primary total knee arthroplasty or total hip arthroplasty, were 6.25 (2.04–19.23) and 6.10 (1.71–21.73), respectively, for any use PPIs compared with non-users. Crude and adjusted ORs, were 11.6 (2.93–45.88) and 17.1 (2.41–121.66), respectively, for patients with a Proportion of Days Covered (PDC) for PPIs <.5 (Table 2). In addition, the crude and adjusted ORs of undergoing revision surgery, were 5.05 (1.59–16.02) and 5.01 (1.36–18.44), respectively, for patients with a PDC for PPIs ≥.5. **Discussion:** These results suggest that PPIs should be used with caution in patients with TKA and THA, and that the use of these drugs should not be prolonged unless there was a justifiable indication. **Conclusions:** The use of PPIs and was associated with a higher risk of early aseptic loosening in patients subjected to THA and TKA.

Keywords

aseptic loosening, proton pump inhibitors, hip, knee, arthroplasty, revision surgery, adult joint replacement

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Introduction

Aseptic loosening is the failure of the bond between a prosthetic implant and bone in the absence of infection. It is the most common cause of revision surgery in total knee arthroplasty (TKA) and total hip arthroplasty (THA), representing about 35% and 55.2% of the cases, respectively.[1,2] These are complex procedures which are frequently associated

significant morbidity, high economic cost, and poorer clinical results compared with primary arthroplasties.[3-5]

The amount of wear debris released from the joint articular surface following an arthroplasty procedure is a major factor influencing the survival of the implants.[6] However, the process of aseptic loosening involves other physical, biologic,[7,8] genetic, surgical-, and prosthesis-related factors.[9] At the center of this process is the activation of receptor activator of nuclear factor κB (RANK)/RANK ligand (RANKL) axis.[10,11] The activation of RANK leads to an increase in osteoclastic activity at the bone-implant interface, which eventually leads to osteolysis.[12]

On the other hand, proton pump inhibitors (PPIs) are widely prescribed among patients suffering ulcers, other gastrointestinal (GI) diseases, and as GI-bleeding-prophylaxis in patients taking non-steroidal anti-inflammatory drugs (NSAIDs). Recent reports estimate that approximately the use of PPIs in the general population in developed countries ranges from 4.0% to 15.5%.[13,14] However, there is growing concern related to the potential adverse side effects of PPIs on bone. Research has shown that that PPIs could impair fracture healing in rats, by the reduction of bone morphogenetic protein (BMP)-2, BMP-4, and cysteine-rich protein (CYR61).[15] Various reports have shown an association between the use of PPIs and an increase in the fracture risk in the general population.[16,17] Moreover, a recent study reported higher non-union rates in patients with femoral and tibial shaft fractures who were treated with PPIs for prolonged periods.[18] Another study observed a decrease in titanium-bone interface osseointegration in rats treated with omeprazole.[19] Moreover, the use of PPIs has been associated with higher non-unions following cervical spine fusion procedures.[20] However, the relation between the use of PPIs and the development of aseptic loosening in TKA and THA has not been studied yet. Accordingly, the objective of this study is to analyze the relation between the use of PPIs, and the risk of aseptic loosening in THA and TKA.

Materials and Methods

Data Source

We designed a nested case-control study on patients how underwent THA or THA in our center between 2010 and 2014. Hospital records were reviewed using our institutional database. Approval from the ethical committee of the Hospital Regional Universitario de Málaga was obtained in order to conduct this study. The guidelines of the World Medical Association[21] Declaration of Helsinki for research involving Human Subjects were followed.

Case Definition

Patients subjected to revision surgery of a primary TKA or THA because of aseptic loosening between 2010 and 2014 were considered as eligible cases. All the patients subjected to THA were operated through a Hardinge's approach. Cases underwent THA using uncemented femoral stems and acetabular components (CORAIL/PINNACLE hip system®, DePuy Orthopaedics, USA). A ceramic-highly crosslinked-polyethylene–bearing surface was used in all cases. On the other hand, we only included patients who were implanted hybrid, (i.e., cemented tibial component and an uncemented femoral component) cruciate retaining (CR) or posterior stabilized (PS), TKAs (Triathlon® total knee system, Stryker Orthopaedics, USA). Aseptic loosening was diagnosed by a combination of clinical symptoms (i.e., persistent groin or knee pain), and imaging (i.e., presence of osteolysis and subsidence on plain x-rays and a positive bone gammagraphy), Aseptic loosening was also confirmed intraoperatively. Infection was ruled-out by 2 intraoperative negative cultures. Individuals known to have a history of prosthetic infections, metal allergies, haemophilia, peri-prosthetic fractures, patellar instability, recurrent total hip dislocations, broken prosthetic components, incomplete medical history, or subjected to an inadequate surgical technique were excluded from this study. Individuals with a history of alcoholism, and malignant tumors were also excluded, as well as patients treated with beta-blockers, anticonvulsants, corticosteroids, or anti-osteoporosis drugs.

The following variables were withdrawn from our database: Data Body Mass Index (BMI), Charlson´s Comorbidity Score (CCS), smoking status (none, current), and history of diabetes mellitus (DM). Cases were followed from the time of primary surgery (i.e., index date) to the time of the revision surgery.

Control Definition

We defined controls as subjects who underwent TKA or THA during the study period, who were not subjected to any type of revision procedure. The same exclusion criteria were applied on controls. Cases were matched with controls in a 1:4 ratio by sex, age (+/− 2 years), follow-up time (±6 months) and type of primary surgery (THA/TKA). All the selected controls for the matching process were alive at the end of the study period. Controls´ follow-up time extended from the index date to the review of the data (i.e., between January 2016 and April 2016).

Exposure Assessment

We reviewed the use of PPI (i.e., omeprazole, lansoprazole, and pantoprazole) at the time of the primary joint replacement in cases and controls. Patients who did not receive PPIs after surgery were considered non-users. Adherence was assessed using the Proportion of Days Covered (PDC) during the follow-up period. The PDC is

determined by dividing the total number of days the patient took a certain medication on total follow-up time. Accordingly, patients were divided into three different groups (i.e., non-users, PDC <.50, and PDC ≥.50).

Statistical Analysis

Data were analyzed with SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). Mean values were expressed with their corresponding standard deviations. The distribution of continuous variables was tested using the Shapiro–Wilk test. Odd ratios were presented with 95% coefficient intervals. Differences between continuous variables were analyzed using Mann Whitney U test or students-t test. Differences between binary variables were analyzed using the Chi square test. Results were considered significant when two-tailed P values were <.05. A binary logistic regression analysis was performed to assess the effect of PPIs on the risk of suffering aseptic loosening. Accordingly, odds ratios for prosthetic revision surgery were adjusted for the following potential confounders: BMI, CCS, and smoking status.

Results

A total of 2105 patients were subjected to primary hip or knee replacements during the study period, from which 107 subjects required revision surgery. After the application of the inclusion and exclusion criteria, we managed to match 29 cases with 116 controls (Figures 1 and 2). The demographic features of the study groups are presented in Table 1.

The mean age of cases and control was 69.1 ± 6.4 and 69.3 ± 6.3, respectively. The male:female ratio was .61 in both groups. Charlson´s comorbidity score in cases and controls was 3.9 ± 1.7 and 3.2 ± 1.4, respectively. Sixty-nine percent of the cases underwent TKR, and 31% were subjected to THR, these percentages were the same in the control group. The mean follow-up time from the index date was 35.8± 16.1 months in cases and 36.2 ±4.8 months in controls. No significant demographical differences were found between the two groups (Table 1). The overall use of PPIs was of 25 (86.2%) in cases and 58 (50.0%) in controls. Omeprazole was the most used PPI in both

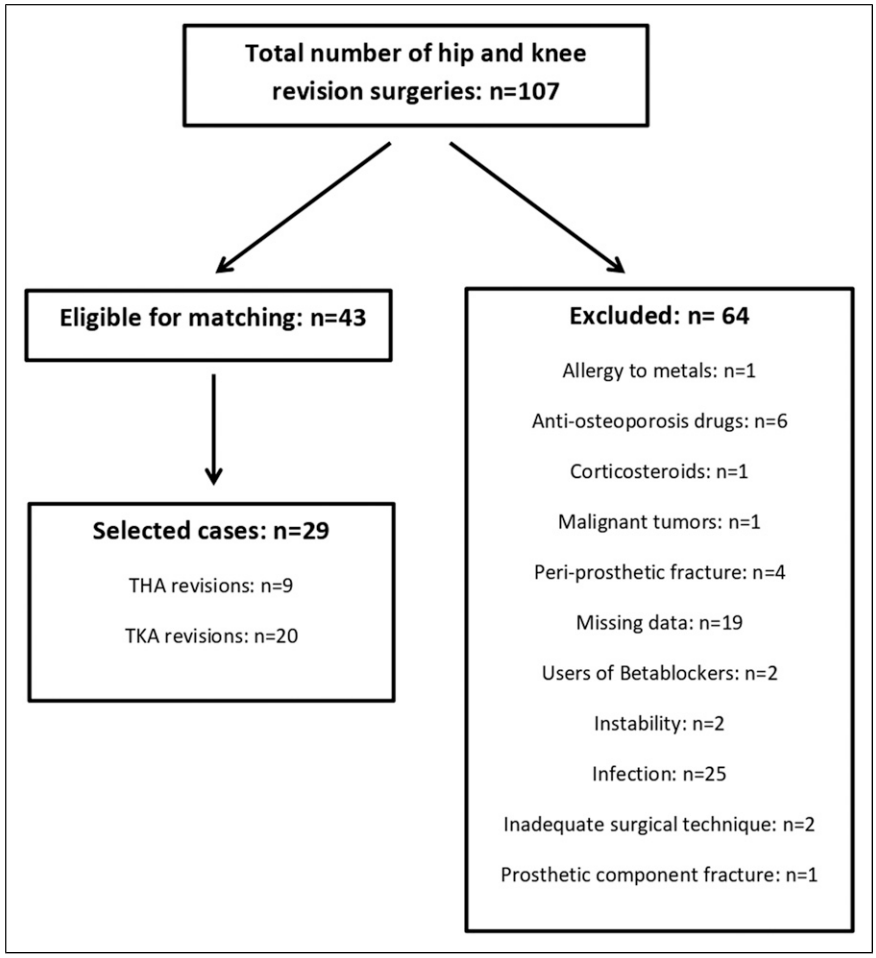

Figure 1. Flowchart describing case selection.

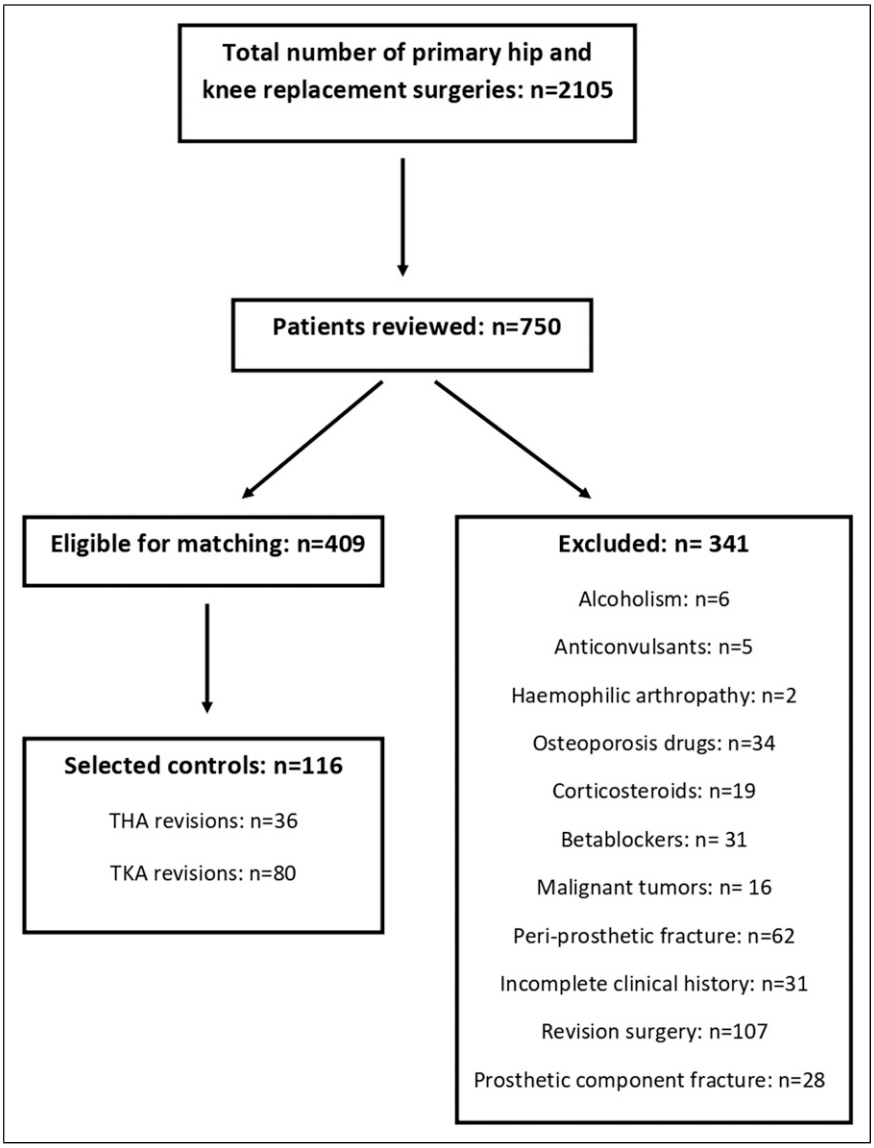

Figure 2. Flowchart describing control selection.

groups [21 (84.0%) in cases vs. 52 (89.6%) in controls] followed by pantoprazole [3 (12.0%) in cases vs. 2 (3.4%) in controls] and lansoprazole [1 (4.0%) in cases vs. 3 (5.1%) in controls] (Table 1).

The crude and adjusted ORs (95% CI) of undergoing revision surgery for aseptic loosening following primary TKR or THR, were 6.25 (2.04–19.23) and 6.10 (1.71–21.73), respectively, for any use PPIs compared with non-users (Table 2). Crude and adjusted ORs were 11.6 (2.93-45.88) and 17.1 (2.41 – 121.66), respectively for patients with a PDC for PPIs <.5 (Table 2). In addition, the crude and adjusted ORs of undergoing revision surgery were 5.05 (1.59–16.02) and 5.01 (1.36–18.44), respectively, for patients with a PDC for PPIs ≥.5 (Table 2).

Discussion

This study provides the first clinical evidence suggesting that the use of PPIs could be associated with a higher risk of early aseptic loosening in THA and TKA. Two recent metanalyses have estimated that the current 25-year survival rates for THA and TKA are around 58% and 82%, respectively.[22,23] Early implant failures are considered those that fail within the first 5 years postoperatively.[24] In this study, the overall early failure rate was 5.1%, from which 40.2% were secondary to aseptic loosening. Fehring et al[24] reported that in TKA, 38% of the early failures were because of infection, 27% because of instability, 13% because of osseointegration failure,

Table 1. Demographic features of cases and controls.

	Cases (n=29)	Controls (n=116)	P Value
Age, years	69.1 ± 6.4	69.3 ± 6.3	.895
Gender	11 (37.9)	44 (37.9)	1.000
Males			
Females	18 (62.1)	72 (62.1)	
Charlson´s score	3.9 ± 1.7	3.2 ± 1.4	.167
Diabetes mellitus	6 (20.7)	25 (21.6)	.991
Joint replacement	20 (69.0)	80 (69.0)	1.000
TKR			
THR	9 (31.0)	36 (31.0)	
Side	21 (72.4)	61 (52.6)	.062
Right			
Left	8 (27.6)	55 (47.4)	
BMI, kg/m^2	29.8 ± 5.5	32.6 ± 4.8	.361
Smokers No	26 (89.7)	110 (94.8)	.384
Yes	3 (10.3)	6 (5.2)	
Follow-up	35.8 ± 16.1	36.2 ± 4.8	.417
Use of PPIs	25 (86.2)	58 (50.0)	.001*
Omeprazole	21 (84.0)	52 (89.6)	
Pantoprazole	3 (12.0)	2 (3.4)	
Lansoprazole	1 (4.0)	3 (5.1)	

Abbreviations: total knee replacement, TKR; total hip replacement, THP; body mass index, BMI; proton pump inhibitors, PPIs.
Data presented as percentages No. (%).
*Statistically significant.

matrix and hematoma.[27,28] Platelets present within the blood clot then begin a cascade of aggregation resulting in a fibrin matrix that acts as a scaffold for the migration, proliferation, and differentiation of white blood cells and mesenchymal cells to the bone-implant gap.[26] During the bone formation phase, angiogenesis takes place and mesenchymal cells differentiate into osteoblasts forming a layer of woven bone.[29] Trabecular bone is then formed around acting as a bridge-like architecture resulting in an active fixation of the implant.[29] Peri-implant bone remodeling takes place through the osteoclastic resorption of woven bone and the formation of lamellar bone. Osteoclasts adhere to the mineralized matrix and deposit bone directly on the implant surface. The lamellar bone provides additional fixation to the implant through biological bonding.[30] After 3 months, the bone implant gap is formed of a mixture of woven and lamellar bone. However, the osseointegration process may take more than a year to be complete.[26] Accordingly, the long-term survival of an arthroplasty would depend on an adequate osseointegration at the bone-implant interface.[31] The failure of the osteogenic process during osseointegration may be due to a decrease in the number or activity of the osteogenic cells, an increased osteoclastic activity, micromotion at the bone-implant interface, and due to an imbalance between the factors regulating bone formation and resorption.[26]

Table 2. Relation between use of PPI and risk of aseptic loosening.

Use of PPIs	Cases a (n=29)	Controls (n=116)	Crude Odd Ratio	Adjusted Odd Ratio ¥
Non-users	4	58	1	
Any use after surgery	25	58	6.25 (2.04–19.23)*	6.10 (1.71–21.73)*
PDC <0.5	8	10	11.6 (2.93–45.88)*	17.1 (2.41–121.66)
PDC ≥0.5	17	48	5.05 (1.59–16.02)*	5.01 (1.36–18.44)*

Abbreviations: proton pump inhibitors, PPIs; Proportion of Days Covered, PDC, body mass index.
Data presented as percentages No. (%).
*Statistically significant.
Matched by gender, prosthesis type, and age.
¥ Adjusted to Charlson´s score, smoking status, and BMI.

7% because of excessive wear, and 22% because of patellar issues.

The Osseointegration Process

Osseointegration is the direct anchorage of a metallic implant into bone tissue.[25] This process consists of three stages: the initial tissue response to the implant, peri-implant bone formation, and peri-implant bone remodeling.[26] The initial tissue response commences after the insertion of the metallic implant into the bone bed. This initial trauma generates an inflammatory response and the release of growth factors and cytokines forming an extracellular

Proton Pump Inhibitors and Bone

The results of this study suggest that PPIs could increase the risk of aseptic loosening following hip and knee arthroplasties. This negative effect was observed in patients with a PDC ≥.5 and in those with a PDC <.5. These results suggest that PPIs could potentially interfere with the early and late stages of bone remodeling.[26] Recent research has shown a significant reduction in the number of osteoclasts in tibial bone defects in rats exposed to omeprazole.[19] This could be probably attributed to a decrease in the expression of certain genes associated with osteoclastic activity such as c-myc, c-src, TRAP, and CATK.[19] PPIs are also known

to increase the expression of osteocalcin and the osteoprotegerin/RANKL ratio and therefore down regulate osteoclastic activity.[32,33] Moreover, the local administration of omeprazole delays the resorption of bone graft materials in animal models through the inhibition of osteoclastic activity[34] [53]. Osteoclast plays a central role in the osseointegration process, especially during the peri-implant osteogenesis and bone remodeling phases.[26] Therefore, PPIs-induced osteoclastic down regulation during these phases could potentially interfere with the osseointegration process. However, bisphosphonates, and beta-blockers which are also known to inhibit osteoclastic activity, have been found to increase the implant survival in patients subjected to lower extremity arthroplasties.[35-37] This paradox suggests that other potential bone metabolic pathways could be involved in the PPI-mediated inhibition of the osseointegration process.

Previous research has shown that the gastric acid suppression induced by PPIs results in hypochlorhydria and consequently reduced serum calcium levels.[38] Moreover, PPIs could also cause a reduction in vitamin D levels.[39] Another study reported that the use of PPIs could induce G-cells in the stomach to oversecrete gastrin, which has been related with hyperparathyroidism.[40] Animal studies have shown that chickens treated with omeprazole developed hypergastrinemia and hypertrophy of the parathyroid glands, resulting in a reduction of their bone mineral density.[41,42] A clinical study performed on patients with gastric ulcers who were treated with PPIs revealed that the parathyroid hormone levels (PTH) increased by 28%.[43] Other studies have reported that PPIs could decrease the expression of bone growth factors such as BMP-2 and BMP-4 [44,45]. In a study performed on human osteoblasts in vitro, PPIs significantly increased osteoblast viability, suggesting that impaired osteoblast function is not the cause of the higher fracture risk in patients treated with PPIs.[46]

The contradicting results on the effects of PPIs on bone do not help to explain their effects on bone fracture and osseointegration.[26] However, the higher rates of THA and TKA aseptic loosening in users of PPIs observed in this study could be probably attributed to a combination of the following factors: inhibition of osteoclast-mediated-peri-implant remodeling, decreased bone formation by BMP-2 and BMP-4 down regulation, and higher bone resorption mediated by increased PTH secretion. Nevertheless, these results suggest that PPIs should be used with caution in patients with TKA and THA, and that the use of these drugs in these patients should not be prolonged unless there was a justifiable indication.

Strengths and Limitations

This nested case-control study was the first specifically designed to assess the association between aseptic loosening in THA and TKA and use of PPIs. Moreover, our analyses of odds ratios were adjusted to several confounders that may affect the results of our study such as body mass index, smoking status, side, and Charlson's comorbidity index. However, our study is also subjected to several limitations. This study cannot establish a causality relation between PPIs and the risk of aseptic loosening because of its observational and retrospective design. Moreover, THA loosening may be caused by different factors compared to TKA loosening; for example, diabetes and weight have been found to have an influence of THA survival but not on the risk of aseptic loosening in TKA.[47] However, to overcome this potential bias, cases were matched by the joint replacement type. In addition, the sample size was relatively small, and the regression analysis did not include other variables that could be related with aseptic loosening such as diet, the level of physical activity, or the use of non-steroidal anti-inflammatory drugs. However, the effect of PPIs on the aseptic loosening rates was already clear in the crude analysis before adjustment to several potential confounders. Nevertheless, despite being less exposed to PPIs patients with PDC <.5 had higher adjusted ORs for aseptic loosening than those with a PDC ≥.5. This notably higher rates in the PDC <.5 group are probably because of the smaller sample size in this subgroup.

Our strict inclusion and exclusion criteria, the matching process, and the binary logistic regression analyses ensure the comparability of the groups.

Conclusions

The use of PPIs was associated with a higher risk if aseptic loosening in THA and TKA. These results suggest that PPIs should be used with caution in patients with TKA and THA, as higher rates of aseptic loosening were obverted in patients with both low and high adherence. These results could guide future research on the effects of PPIs on patients undergoing joint replacement surgery.

Declaration of Conflicting Interests

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