Journal of Infectious Diseases and Therapy
ISSN: 2332-0877

Barbero, et al., J Infect Dis Ther 2014, 2:6
DOI: 10.4172/2332-0877.1000177

Research Article Open Access

Can too Much Antibiotic Prophylaxis in Arthroplasty Surgery be Harmful? Results of a Series of Cases Study

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Rec date: August 28, 2014; **Acc date:** October 22, 2014; **Pub date:** October 29, 2014

Abstract

Background: Preoperative antibiotic prophylaxis has been shown to decrease the incidence of surgical wound infection. Prosthetic joint infection (PJI) is a type of surgical wound infection with serious consequences.

Objective: The purpose of this study is to evaluate whether expanding the antibiotic prophylaxis with repeated doses in the postoperative period may lead to an increase in the incidence of PJI.

Patients and methods: We retrospectively analyzed 556 patients undergoing hip or knee primary arthroplasty in our hospital between January 1, 2009 and December 31, 2010. All the patients received a preoperative dose of an antibiotic and 164 patients also received at least one additional dose after surgery.

Results: There were 16 PJI (incidence of 2.9%). PJI occurred in 7/94 patients with repeated doses of antibiotics after surgery (7.4%), compared to 9/462 (1.9%) in patients who only received the preoperative dose (odds ratio [OR] 3.1, confidence interval [CI] 95% 1.1 to 9.4, p=0.04).

Conclusions: In our study, the patients who received antibiotics after surgery were at greater risk of developing PJI.

Keywords: Antibiotic prophylaxis; Prosthetic joint infection; Surgical wound infection

Introduction

Arthroplasty has achieved significant improvements in the functional capacity of patients with arthropathy. The aging of the population and technological breakthroughs have made it a procedure that has become markedly more popular. It is estimated that 300,000 prosthetic joints are implanted annually in Spain [1], and in the U.S. estimates suggest that about 4.5 million arthroplasties will be performed in 2030 [2]. Although PJI is a rare complication, this increase will invariably entail more infections.

There are significant variations in the incidence of PJI in the published studies. Most publications mention an incidence of between 1 and 2% [3-6], while in Spanish studies, it raises to 2-5% [7-10]. The risk factors associated with PJI also vary depending on the studies consulted. They include prior surgery on the joint [5,11], immunosuppression [3,11], the presence of a malignant disease [3], the anesthetic risk [6,11], the duration of surgery [4,11], diabetes mellitus (DM) [9,12], obesity [6,11,12], perioperative transfusions6, the duration of urinary catheterization [7], postoperative urinary infection [6,13], the surgical-site infection risk index [3] and rheumatoid arthritis [5].

Surgical wound infection is the second most common nosocomial infection [14]. The perioperative administration of antibiotics has proven effective in preventing wound infection in traumatology [15] and orthopedic surgery [16], as well as in gastrointestinal [17], cardiac [18], thoracic [19] and urologic surgeries [20]. There is also evidence that the antibiotic must be administered before the start of surgery so that it reaches a sufficient concentration at the site of the wound when the incision is performed [21,22]. However, studies to determine whether to maintain postoperative antibiotic prophylaxis have not shown any additional benefit [23]. Nonetheless, it is common practice among some surgeons to prolong antibiotic therapy in surgery considered to have an excessive risk of infection.

In this paper, we analyze the incidence of PJI in patients undergoing hip or knee prosthesis in our hospital who received repeated doses of post-operative antibiotic prophylaxis.

Patients and Methods

We performed a retrospective study of patients undergoing hip and knee primary elective arthroplasty in our hospital between January 1, 2009 and December 31, 2010. The Principe de Asturias University Hospital of Alcalá de Henares (Madrid) is a second-level academic hospital with 600 in-patient beds. It serves a population of 450,000 people, and is a training center for the Faculty of Medicine of the University of Alcalá de Henares.

We included all patients who underwent elective primary arthroplasty and excluded revision surgeries. The minimum follow-up period was 12 months.

We excluded revision arthroplasty, post-traumatic artrosis, history of any infection within the preceding 2 months, history of an

operation in the same hip or knee for other causes, known history of allergy to the studied drugs, pregnancy or lactation and any antibiotic therapy in the week before operation.

In our hospital, the antibiotic prophylaxis protocol used in arthroplasty surgery is one dose of cefazolin 30-60 minutes before the beginning of surgery, or 1 gram of vancomycin one hour beforehand if the patient is allergic to beta-lactams. No additional doses are specified.

The diagnostic criteria used for diagnosis of PJI were the most comunes: purulent synovial or periprosthetic fluid, more than 5 leukocytes per high-power field in the synovial biopsy, presence of ntra-articular fistulae or isolation in 2 or more microorganism samples (only one for *S. aureus*) [24]. Those who developed PJI in the first 12 months after surgery were included as cases.

We reviewed the patients' clinical records and collected the following data: age, sex, presence of DM, obesity or rheumatoid arthritis, comorbidity measured by the Charlson index, anesthetic risk according to the ASA classification, risk of infection according to the NNIS system, number of transfusions, days of urinary catheterization, incidence of postoperative urinary infection and the number of doses of perioperative antibiotics received. The definitions of the risk factors are listed in Table 1.

Risk factor	Definition
Diabetes mellitus	As defined by American Diabetes Association [25]
Obesity	Body mass index greater 30% [26]
Rheumatoid arthritis	As defined by American Rheumatism Association [27]
Comorbidity	As defined by Charlson index [28]
ASA Index	As defined by American Society of Anesthesiologits [29]
NNIS Index	As defined by CDC [30]
Urinary infection	>10 WBCs per high-power field or bacteriuria plus urinary symptoms [31]
Blood transfusions	Any heterologous blood transfusion after the surgery and before the hospital discharge (excluded autotransfusion and cell savers during surgery)
ASA: American Society of Anesthesiologists; CDC: Center for Disesase Control and Prevention; NNIS: National Nosocomial Infection Surveillance System; PJI: Prosthesis Joint Infection; WBC: White Blood Cells.	

Table 1: Definitions of potential risk factors for PJI.

Statistical Analysis

The quantitative variables are described with a mean confidence interval of 95%. The categorical variables are expressed as a percentage. The mean differences were analyzed by the Student t test and the categorical variables were analyzed by calculating the OR. The multivariate analysis was performed using logistic regression. The variables were entered into the model using the stepwise inclusion method. The inclusion and exclusion criteria for the variables in the model are set at $p<0.05$ for inclusion, and $p>0.10$ for exclusion. The calibration of the model was evaluated using the Hosner-Lemeshow goodness of fit test. Statistical significance was set at $p<0.05$. All the calculations were performed using the SPSS 15.0 program (Chicago, USA).

Results

During the period mentioned above, 556 prostheses were implanted in 554 patients (360 women, 65%). In all surgeries, patients received a single dose of preoperative antibiotic and 94 (16.8%) also received at least one extra dose in the postoperative period (mean 6.2, CI 95% 5.4 to 7). A total of 16 patients developed PJI (incidence of 2.9%).

Table 2 shows the characteristics of the cases of PJI compared to the controls without PJI. The univariate analysis showed significant differences in comorbidity, rheumatoid arthritis, duration of surgery, NNIS index, duration of urinary catheterization, number of transfusions and multiple dose regimen of antibiotic prophylaxis.

	No PJI (n=540)	PJI (n=6)	Difference/OR	p value
Age (CI 95%)	67.6 (66.8 to 68.5)	68.5 (59.8 to 77.2)	0.9 (-4.1 to 5.8)	ns
Charlson índex (CI 95%)	3.8 (3.6 to 3.9)	4.6 (3.6 to 5.7)	0.8 (0.1 to 1.6)	0.02
Diabetes mellitus (%)	104 (19.3%)	3 (18.8%)	OR 1 (0.3 to 3.4)	ns
Obesity (%)	275 (50.9%)	9 (56.3%)	OR 1.2 (0.7 to 2.3)	ns
Rheumatoid arthritis (%)	14 (2.6%)	2 (12.5%)	OR 5.4 (1.1 to 25.8)	0.04
Hip (%)	142 (26.3%)	2 (12.5%)	OR 3.1 (0.7 to 13.4)	ns

Knee (%)	398 (73.7%)	14 (87.5%)		
Duration (min) (CI 95%)	101.7 (99.3 to 104.1)	131.3 (88.1 to 174.4)	29.6 (14.1 to 45)	<0.001
ASA index (%)	27 (5)	1 (6.2)	OR 1.3 (0.2 to 9.9)	ns
	365 (67.6)	12 (75)	OR 1.4 (0.5 to 4.5)	ns
	145 (26.9)	3 (18.8)	OR 0.6 (0.2 to 2.2)	ns
	3 (0.6)	0	OR 0.2 (0.01 to 4.4)	ns
NNIS index (%)	320 (59.3)	6 (37.5)	OR 0.4 (0.1 to 1.2)	ns
	189 (35)	10 (62.5)	OR 3.1 (1.1 to 8.6)	0.03
	31 (5.7)	0	OR 0.5 (0.03 to 8.3)	ns
Days of urinary catheter (CI 95%)	2 (1.9 to 2.1)	2.7 (2.1 to 3.3)	0.7 (0.1 to 1.2)	0.02
Urinary infection (%)	16 (3%)	1 (6.2%)	OR 2.2 (0.2 to 17.5)	ns
Transfusion (number of units) (CI 95%)	1.2 (1.1 to 1.4)	2.2 (0.7 to 3.8)	1 (0.3 to 1.7)	0.006
Patients with multiple antibiotic doses (%)	86 (15.9%)	7 (43.3%)	OR 4.1 (1.5 to 11.2)	0.007
ASA: American Society of Anesthesiologists; CI: Confidence Interval; NNIS: National Nosocomial Infection Surveillance System; OR: Odds Ratio; PJI: Prosthesis Joint Infection.				

Table 2: Characteristics of cases with PJI and their controls without PJI; Univariant analysis.

With the logistic regression analysis, PJI was more common in the multiple dose group (7/94) than in the preoperative single dose group (9/462, 7.4% vs. 1.9%, OR 3.1, CI 95% 1.1 to 9.4.57, p=0.04).

Patients were more likely to receive multiple postoperative doses of antibiotics if the surgery was of a prolonged duration, or in cases with a rheumatoid arthritis, high NNIS index, longer urinary catheter duration or with more transfusions (Table 3).

The most common causative microorganism was *S. aureus* with 7 cases (43.8%, 4 methicillin-resistant), followed by S. epidermidis with 5 cases (31.3%) and Enterococcus spp with 2 cases (12.5%). Gram-negative bacilli were involved in 4 cases (25%). The infection was polymicrobial in 5 cases (31.3%).

	Repeated dose	**One dose**	**OR (CI 95%)**	**p value**
Incidence PJI (%)	7/94 (7.4%)	9/462 (1.9%)	3.1 (1.1 to 9.4)	0.04
CI: Confidence Interval; PJI: Prosthesis Joint Infection; OR: Odds Ratio.				

Table 3: PJI incidence in multiple antibiotic doses group vs single dose group; Multivariant analysis.

Discussion

Our results show that in arthroplasty surgery, prolonged antibiotic prophylaxis after surgery is no better than a single preoperative dose, and may even be harmful and increase the risk of PJI.

PJI are classified according to the period of time elapsed since their inception. This paper focuses on the study of PJI that occur within the first 12 months (acute and delayed), i.e. those which are assumed to have been acquired at the time of surgery or in the immediate postoperative period [32]. The incidence is known to be influenced by several perioperative factors. It is possible to establish prevention strategies if we know what these factors are.

The studies of PJI present significant differences as regards incidence, risk factors and microbiology. Most North American studies have been produced by experienced centers, some of which are single-purpose hospitals [3-6,12], which may explain the lower incidence in Spanish publications [7-10].

The studies also vary in terms of the risk factors related to PJI. The absolute number of cases of PJI is low, and few studies are multicentric [6]. This is possibly the reason why the differences between cases and controls were not always statistically significant (e.g. DM and perioperative transfusions are significant in some studies and not in others [8,11,13], i.e. it is possible that many studies are statistically underpowered.

Our study is consistent with others as regards duration of surgery [7], rheumatoid arthritis [24], high NNIS3, duration of urinary catheterization4 and transfusions [9,13]. Nevertheless, statistical significance was not reached in DM or obesity, unlike the other larger studies [12]. This is possibly due to the lower statistical power because of the small number of cases.

After demonstrating the effectiveness administering a single dose of antibiotics before surgery to reduce the incidence of surgical infection [15-20,33], several studies have failed to demonstrate the usefulness of extending their duration in the postoperative period [23,34,35]. The international recommendations therefore advise using a single preoperative dose in clean surgery [36]. Nonetheless, it is common clinical practice among some surgeons to prolong the duration of antibiotic therapy in cases in which they subjectively consider that there is a greater risk of infection. Moreover, they do so using different patterns, without any scientific evidence (three doses, three days, until the urinary catheter is removed, etc.).

In our study, patients receiving multiple doses of antibiotic prophylaxis had a higher risk of PJI. It is true that this group contains a higher proportion of patients with prolonged surgeries and it could be a bias. For this reason, these patients were thus more likely to receive several doses of antibiotics higher NNIS index, with larger transfusions or more days with a urinary catheter (Table 4). However, the difference remains after adjustment for these factors in the multivariate analysis.

	One dose (n=462)	Repeated dose (n=94)	Difference/OR	p
Age (CI 95%)	67.6 (57.8 to 77.5)	67.5 (56.8 to 78.2)	-0.1 (-2.4 to 2)	ns
Charlson index (CI 95%)	3.7 (2.3 to 5.2)	3.8 (2.3 to 5.4)	0.1 (-0.2 to 0.4)	ns
Diabetes mellitus (%)	94 (20.3)	13 (13.8)	OR 0.6 (0.3 to 1.2)	ns
Obesity (%)	325 (51.6%)	51 (54.3)	OR 1.1 (0.7 to 1.5)	ns
Rheumatoid arthritis (%)	10 (2.2)	6 (6.4)	OR 3.1 (1.1 to 8.7)	0.03
Hip (%)	120 (26)	25 (26.6)	OR 0.9 (0.6 to 1.6)	ns
Knee (%)	342 (74)	69 (73.4)		
Duration (min)	100.6 (75.3 to 125.9)	112.3 (61.6 to 162.9)	11.7 (4.8 to 18.6)	0.01
NNIS index (%): 0	273 (59.1)	52 (55.3)	OR 1.2 (0.8 to 1.9)	ns
1	169 (36.6)	31 (33)	OR 0.8 (0.5 to 1.4)	ns
2	20 (4.3)	11 (11.7)	OR 1.7 (1.2 to 2.5)	0.006
Days of urinary catheter (CI 95%)	2.2 (2.1 - 2.3)	2.7 (2.3 - 3)	0.5 (0.2 to 0.8)	0.01
Urinary infection (%)	22 (4.8%)	3 (3.2%)	OR 0.6 (0.2 to 1.6)	ns
Transfusion (number of units) (CI 95%)	1.1 (1 to 1.2)	2.1 (1.6 to 2.5)	1 (0.7 to 1.3)	<0.001
PJI (%)	9 (1.9%)	7 (7.4%)	OR 3.1 (1.5 to 6.5)	0.02

ASA: American Society of Anesthesiologists; CI: Confidence Interval; NNIS: National Nosocomial Infection Surveillance System; OR: Odds Ratio; PJI: Prosthesis Joint Infection.

Table 4: Characteristics of patients with one preoperative dose antibiotic and patients with repeated dose.

A prolonged prophylaxis with antibiotics has been shown to be a risk factor for selecting resistant bacterial flora, and facilitating the colonization of implanted devices [37,38]. In studies of cardiac surgery, patients who received antibiotics for too long had a higher incidence of wound infection and of infection by resistant organisms [35]. Most PJI in the multiple dose group occurred due to microorganisms resistant to the antibiotics used in the prophylaxis (Table 4).

The study is limited by its retrospective, observational, single-center nature. The patients are not randomized, which would affect the variability of the results, although the multivariate analysis may establish a relationship. The results of this study should be confirmed in a randomized double-blind study. Nonetheless, clinical trials in orthopedic surgery have already shown a lack of benefit [39,40] and the worsening cost-benefit relationship in the multiple-dose regime [41]. We therefore believe that further studies are needed to demonstrate that in addition to the lack of benefits, prolonging the prophylaxis after surgery could be harmful.

Awareness of the risk factors for PJI can help prevent them by means of implementing the measures that affect them. It is well established that increasing the duration of postoperative antibiotic prophylaxis fails to reduce the rate of infection. We conclude that it may even also be dangerous as it selects resistant flora, and as such should it not be carried out.

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