Title: Incidence and Risk Factors for Acute Infection After Proximal Humeral Fractures: A Multicenter Study

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Abstract

Background. The rate of acute infection after surgery for proximal humeral fractures is not know with certainty. The aims of this study were to report the incidence and analyze the risk factors for infection after treatment for proximal humeral fracture.

Methods. We report a retrospective multicenter study including 452 proximal humeral fractures. Data were modeled using univariate and linear regression analyses where appropriate to determine the ODDS ratio. A logistic regression analysis was employed to control for demographic and other characteristics with the potential to confound a true association between risk factors and infection.

Results. The average age was 62.1 years, 314 were female. Eighteen patients(4%) had an acute infection. The factors that correlated with infection were length of surgery (ODDS 1.009, p=0.05), preoperative lavage with chlorhexidine gluconate (ODDS 0.13, p=0.008) and prophylactic antibiotic (ODDS 10.73, p=0.03). The delay of surgery was close to achieving significance (ODDS 1.71, p=0.06).

Conclusion. This study suggests that washing the shoulder with chlorhexidine gluconate and avoiding the use of first generation cephalosporin in favor of more effective prophylactic therapy are effective at reducing the risk for infection after treatment for proximal humeral fractures.

Level of Evidence: level II, Prognostic Study.

Key words: proximal humeral fracture, osteosynthesis, infection, logistic regression analysis

Introduction

The correct treatment of proximal humeral fractures is still debatable. Of all the arguments that orthopedic surgeons have proposed to support one treatment over another, recent attention has been focused on complication rates[1; 30; 32].

The ideal treatment for a proximal humeral fracture should allow healing of the fracture with a low rate of complications such as malunion, non-union, avascular necrosis and infection. Unfortunately none of the techniques now available have proven to be free of complications[5; 7; 11; 13; 15; 34; 36].

Among all the complications, infection is probably the one that the surgeons fear most. This is because postoperative infections may lead to high rates of revision surgery, long and frustrating months of treatment with antibiotics and, usually in the end, unsatisfied patients[3].

Surprisingly very few papers have been published regarding infection after surgical treatment for proximal humeral fractures. The rate of infection reported ranges from 0% to 8% depending on the techniques and criteria used to define infection[23; 29; 34]. However, the real incidence rate in an wide cohort of patients is still not known. Even less information is available on the potential risk factors for the development of an acute infection. Several variables such as comorbidities[10; 20; 27], age of the patient[9; 27] and delay to treatment[16; 28] have been suggested to play a role in the rate of infection in other joints, but no data are available for the proximal humerus.

The aim of this study was to determine in a multicenter study the incidence of acute infections after surgical treatment of a proximal humeral fractures and to analyze preoperative and intraoperative factors that might affect the rate of infection.

Material and methods

A multicenter study was carried out in the three University hospitals of our region. The data were collected from the electronic database in each hospital using three different information-reporting applications. The electronic database contained clinical records as well as surgical and outpatient information. The records were available starting from 2004 in one hospital and from 2006 and 2010 in the other two hospitals respectively. Data collection was performed independently by three different researchers not involved in the care of the patients. After being instructed by the principal investigator, the researchers screened and collected data regarding patients treated surgically for proximal humeral fractures (ICD-9 treatment codes 78.12, 78.42, 78.52, 79.31, 79.91).

The exclusion criteria were: 1) patients that underwent an hemi- or reverse shoulder replacement, 2) polytrauma cases (defined as AIS>2 in at least two body regions[6]), 3) open fractures, and 4) less than 3 months of follow-up. From this analysis, the study group was selected and the following variables recorded: age, gender, delay from trauma to surgery, antibiotic prophylaxis, type of surgery, type of reduction (open vs closed), length of surgery, type of skin preparation, comorbidities (rheumatoid arthritis, liver failure, heart failure, HIV, Hepatitis C and diabetes mellitus), and concomitant fractures that needed surgical treatment.

The clinical records were reviewed with the purpose of identifying any incidence of acute infection, defined as occurring within three months after the index fracture surgery. An infection for the purpose of this study was defined as an infection with primary involvement of the deltoid and/or humerus and/or gleno-humeral joint. The extent of the diagnosis was established using either ultrasound or MRI. Patients with severe symptoms of infection such as extensive swelling, fever and pain were treated with more than 30 days of oral or intravenous antibiotics. In some of the cases, a second surgery was indicated to eradicate the infection.

A persistent serous drainage from the skin incision or persistent drainage from a pin tract, without significant erythema and wound dehiscence, was not considered an infection. In some of these cases, antibiotics were prescribed, but usually for less than 30 days. These patients were excluded from this study.

A positive culture was not required for the diagnosis of infection when the symptoms were clearly indicative of infection and the patients responded positively to antibiotic therapy. In spite of the potential for this to lead to an overestimation of the rate of infection, this approach was chosen in order to avoid missing those cases of infection that might have presented with negative culture results, due to inadequate cultural time for the identification of *Propionibacterium acnes*[24].

Antibiotic prophylaxis. All the patients received prophylactic antibiotics immediately before surgery. In two hospitals a first generation cephalosporin antibiotic (2 g dose of cefazolin) was the standard of care. In one hospital a third-generation cephalosporin antibiotic (2 g dose of ceftriaxone) was used in all cases. Some exceptions to this were when patients were allergic to cephalosporin and were instead treated with 1g of vancomycin or fluoroquinolone antibiotics. For the statistical analysis the variable ñantibiotic prophylaxisò was organized as follows: a) First generation cephalosporin, b) Third generation cephalosporin, c) Other prophylaxis.

Skin preparation. A standard skin preparation with 1% povidone-iodine and 50% isopropyl alcohol was performed in all the patients. However, in one hospital the preparation was changed after May 2008. In this hospital the skin of the entire upper limb was pre-washed (Figure 1), with the patient under anesthesia, using 4% chlorhexidine gluconate (Neoxidina Mani, Farmec, Settimo di Pescantina (VR) ï ITALY) and then a standard disinfection with 1% povidone-iodine and 50% isopropyl alcohol was performed. This modification was introduced empirically with the intent of providing a cleaner surgical site since most of the patients arrive in the operating room with their arm in a sling or bandage, without having had the opportunity for normal hygiene of the shoulder and axilla.

Surgical technique. Several techniques were used to treat proximal humeral fractures over the course of the study period. Techniques were clustered according to the reduction (open vs closed) and type of fixation (locking plate versus percutaneous fixation versus other techniques). Other techniques included nailing, osteosutures, and screw fixation.

Statistical analysis. A univariate analysis was performed by measuring the ODDS ratio for binary variables (Gender, Type of Surgery, Comorbidities, Other Fractures, Open Reduction, Skin Preparation, Antibiotic Prophylaxis) and using a linear regression analysis for continuous data (Delay to Surgery, Age, Length of the Surgery). Acute infection was considered as dependent variable.

A logistic regression analysis was employed to control for demographic and other characteristics with the potential to confound a true association between risk factors and infection. Risk factors with $p<0.2$ were included in the multivariate logistic regression analysis. An initial nonlinear regression analysis revealed that the infection rate could potentially be associated with a delay of surgery. A *post hoc* analysis was then performed using a segmented regression[19]. Segmented regression analysis is a method of regression analysis used in cases of non-linear correlation between variables. Segmented regression is useful when the independent variables, clustered into different groups, exhibit different relationships between the variables in these regions. The patients were clustered in this manner in two groups according to the breakpoint of the regression model function. Statistical analysis was performed with MedCalc software (Mariakerke, Belgium).

Source of funding. No external funding has been used for this study.

Results

Five hundred and ten patients were initially enrolled in the study. From this cohort, 58 were excluded: 5 died before the minimum follow up of 3 months, and 53, that had a recorded follow up of less than 3 months, could not be traced (most frequently because of an incorrect phone number). In these patients, we could not exclude an acute infection. The remaining 452 patients formed the study population.

The average age at surgery was 62.1 years (SD=16.2, range 14-94 years), 314 (69.5%) were female. The average follow up was 14.5 months (range 3-to-76 months). Two hundred and nine patients (46%) underwent a percutaneous fixation, 197 (44%) patients had an osteosynthesis with a plate and the remaining 46 (10%) were treated with other techniques (including 25 with nails). Three hundred and six fractures underwent an open reduction. The average delay from trauma to surgery was 6.2 days (SD=3.9, range 0-24 days). Forty-one patients had at least one comorbidity and of these, 29 had diabetes mellitus. Twenty-four patients had a concomitant fracture (5%) that was treated surgically. Of the 452 patients, 18 (4%) had a deep infection. The details are reported in Table I. Of the 18 cases of infection, 5 needed a second surgery of which 4 had had a plate fixation and 1 a percutaneous fixation (p=0.047).

In sixteen cases a culture test was performed. In two cases the culture was negative despite the clinical signs and symptoms of infection. In the remaining 14 cases, 8 were positive for coagulase negative *Staphylococcus*, 5 were positive for *Staphylococcus aureus* (of which 3 were methicillin-resistant *Staphylococcus aureus* ï MRSA), one was positive for *Propionibacterium acnes*, one for *Enterococcus* and one for *Corynebacterium*. Two patients had a polymicrobial infection. In two patients the culture test was not collected due to the absence of open wounds or fistulae.

The univariate analysis revealed that the preoperative lavage significantly reduced the risk of acute infection (ODDS ratio 0.8, p=0.026) while the prophylactic administration of first generation cephalosporin increased the risk of having an infection (ODDS ratio 4.7, p=0.13). The type of reduction and fixation and the presence of concomitant fractures or comorbidities did not affect the rate of acute infection. Among the continuous variables, only the length of surgery was potentially associated with rate of infection (p=0.19) (Table II).

After controlling for demographic and other characteristics possibly confounding a true association between risk factors and the development of acute infection, the preoperative lavage confirmed its protective effect against infection (ODDS ratio 0.13, p=0.008) and the prophylactic administration of first generation cephalosporin significantly increased the risk of infection (ODDS ratio 10.73, p=0.03). The length of surgery also increased the risk of infection (ODDS ratio 1.009, p=0.05) (Table III).

***Post-hoc* analysis**

The lowest incidence of infection was observed when the patients underwent surgery within 48 hours of trauma (rate 1.56%). The patients were clustered in two groups according to the breakpoint of the regression model function that was observed at 5 to 6 days after trauma (Figure 2). Two-hundred eighty two patients underwent surgery within 6 days of the trauma. In this subgroup of patients we observed most of the acute infections (12 out of 18). A *post-hoc* analysis in this subgroup of patients confirmed the previous data (Table IV). The length of surgery was found to significantly increase the rate of infection (ODDS ratio 1.02, p=0.02). Within 6 days of the trauma, the delay to surgery was found to be potentially related to the rate of infection (ODDS ratio 1.71, p=0.06).

Discussion

The aims of this study were to measure the rate of acute infection and to search for factors related to the incidence of acute infection after surgical treatment of proximal humeral fractures. This study showed a rate of acute infection of 4%. These data are in line with the rates of infection reported in literature of 0 to 8% depending on the techniques and criteria used to define infection (and probably depending on the sample size as well)[23; 29; 34]. To the best of our knowledge, the only study with a sample size comparable to our report is the one from Athwal G.S. *et al*. Compared to our study they reported a lower rate of infection (2/259 cases, 0.77%) however they included only cases of infection that needed a revision surgery. This could explain the discrepancy between the two studies. In our study we report 18 cases of acute infection, but only 5 needed a second surgery (5/452, 1.1%).

The second main finding of this study was that the preoperative lavage with chlorhexidine, the type of antibiotic prophylaxis and the length of surgery were the factors that most affected the rate of deep infection. Conversely, age, comorbidities, concomitant fractures that needed surgery, gender, type of fixation, and type of reduction (open vs. closed) did not seem to affect the rate of infection.

The delay to surgery was associated to an increased rate of infection within approximately the first week of the trauma with an association that was close to statistical significance. The favorable relationship between acute surgery and infection rate has already been shown for open[8; 18] and closed fractures[16; 33]. Our study supports this observation. The reason behind the increased incidence of infection up to 5-to-6 days after trauma is not clear. The occurrence of hematoma and edema over the course of the first few days from trauma could partially explain the increased incidence of infection. Moreover, between trauma and surgery, patients had to hold the arm in a bandage without the ability to keep the shoulder clean. This could increase the number and type of bacteria in the surgical site and subsequently affect the rate of infection. This second hypothesis seems to be additionally supported by the fact that the type of prophylactic antibiotic as well as the preoperative lavage played a role in the infection rate in our cohort of patients. First generation cephalosporin increased the risk of infection while the preoperative lavage with chlorhexidine gluconate was protective against acute infection, suggesting that bacteria-specific factors and not only patient and surgeon-related factors are important variables to be considered. Even though preoperative bathing or showering with an antiseptic skin wash product is a well-accepted procedure for reducing skin bacteria[35], very few data are available for the shoulder. Saltzman and colleagues have demonstrated that chlorhexidine gluconate is more effective than povidone-iodine in eliminating coagulase-negative *Staphylococcus* from the shoulder region[21]. In our series the most frequent bacteria isolated was the coagulase-negative *Staphylococcus* and all these cases except one were not washed with chlorhexidine gluconate. Interestingly, of the three patients that had an acute infection despite the wash with chlorhexidine gluconate, two had a positive culture for MRSA. The reason behind this association is not known, however, we can speculate that the infection was contracted after the lavage which means intraoperatively or during the postoperative period.

The type of bacteria isolated in this study were similar to the bacteria reported by Athwal G.S *et al*. Their study results showed that the most frequent encountered bacteria involved in the infections on which they reported was coagulase-negative *Staphylococcus*. Contrary to their study we found only one infection due to *Propionibacterium acnes*. However, we cannot preclude the two cases in our series with negative cultures as not being due to *Propionibacterium acnes* that may have not been recognized due to its slow growth in culture.

The correlation between delay to surgery and infection was not linear since the rate of infection slightly decreased after 6 days. This trend suggests that after approximately one week following trauma other unknown factors reduced the rate of infection. Similar benefits related to delaying surgery for more than one week have been reported for tibial plateau fractures and calcaneus fractures[2; 12; 22]. The rationale behind this finding is not known. Sun *et al.*[31] have recently demonstrated that proinflammatory mediators are increased in older patients with a hip fracture and that level correlates with complications including infection. Based on their study, they suggested that ñdamage control orthopedic surgeryò may play a role in reducing complications related to cytokine-associated immunosupression not only in the management of multiple injury patients, but also in simpler fractures as well.

This study was not able to find a significant correlation between comorbidities, including diabetes mellitus, and infection rate. Hyperglycemia has been shown to be an independent risk factor for infection in multiple patient populations including hip fracture[14]. Schmeltz *et al*.[25] found that glucose management with a combined IV and SC insulin regimen eliminates the increased postoperative morbidity and mortality in patients with preexisting diabetes. Most of the patients with diabetes in our study group routinely had a consultation with a diabetes specialist before surgery in order to correct hyperglycemia with an intravenous insulin regimen. This could explain the lack of association between diabetes and infection rate in this study.

The rate of acute deep infection was not different between percutaneous fixation and plate fixation. However, when the patients that underwent a plate fixation were compared with the patients that underwent a percutaneous fixation the rate of second surgery needed to treat the infection was in favor of percutaneous fixation. Of the 5 cases that needed a second surgery, 4 had had a plate fixation and 1 a percutaneous fixation (p = 0.047). This difference can be explained by the fact that most of the patients that were treated with a percutaneous fixation underwent a temporary fixation with an external fixator that is usually removed after 5 to 6 weeks following the surgery[4]. In these patients no hardware is left in the shoulder, simplifying the treatment of the infection. Similar conclusions have been reported by Shabtai *et al*[26] in a series of 46 patients with a proximal humeral fracture treated with an external fixator.

Interestingly, we found that the length of surgery was related to the rate of infection more than the type of reduction and fixation. This finding implies that strategies to reduce the surgical time can be effective in reducing the risk of infection. Referral of proximal humeral fractures to a few high volume centers could be one way to capitalize on increase the level of expertise and subsequently reduce the duration of surgery. Similar results have been found for knee replacement and infection rate [17]

This study has some limitations. The main limitation is the retrospective nature of the study. Not all the potential risk factors for infection have been investigated. Other factors such as the smoking habits of the patients could play an important role. However, these data were not available in the database for review. One should be mindful of these limitations when considering the results of this study.

Conclusions

This study suggests that preoperative lavage with chlorhexidine gluconate, length of surgery and type of prophylactic antibiotic play an important role in the rate of acute deep infections after surgical treatment for proximal humeral fracture.

In light of these results we suggest washing the shoulder with chlorhexidine gluconate and to avoid use of first generation cephalosporin in favor of a more effective prophylactic therapy such as third generation cephalosporin or vancomycin. With the data available we cannot suggest operating within 48 hours of trauma. Although some evidence exists in this direction, more studies are needed. Operating on proximal humeral fractures within 48 hours would require and extensive re-organization of most hospitals and, with the data available, would be premature.

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Legends

Figure 1: relationship between rate of acute infection and delay to surgery. The correlation between delay to surgery and infection was not linear since the rate of infection slightly decreased after 6 days.

Table I: list of cases with infection. MRSA

Table II: risk Factors

Risk factors in bold had a p value less that 0.02 and were included in the logistic regression analysis.

Table III: logistic regression analysis

Table IV: post-hoc analysis (days 0-to-6)

Table I: list of cases with infection. MRSA
F: female; M: male; MRSA: Methicillin-resistant *Staphylococcus aureus*

N°	***Gender***	***Age***	***Comorbidity***	***Lenght (min)***	***Surgery***	***Delay to Surgery***	***Pre-operative wash***	***First generation Cephalosporin***	***Cultural***	***Treatment***
1	M	27	No	120	Percutaneus Fixation	5	No	No	CoNS	Open debridment
2	M	38	No	200	Locking plate	4	No	Yes	*Propionibacterium acnes*	Open debridment + plate remuval
3	F	40	No	180	Locking plate	6	No	Yes	Not performed	Antibiotics
4	F	43	Reumatoid Arthritis	45	Percutaneus Fixation	7	No	Yes	**MRSA**	Antibiotics
5	F	59	No	120	Percutaneus Fixation	4	No	Yes	Not performed	Antibiotics
6	F	60	No	90	Locking plate	5	No	Yes	*Enterococcus spp.*	Antibiotics
7	F	60	No	98	Locking plate	9	No	Yes	Negative	Open debridment + plate remuval + reverse shoulder replacement
8	F	62	No	90	Percutaneus Fixation	5	No	Yes	CoNS	Antibiotics
9	F	64	No	30	Percutaneus Fixation	11	Yes	Yes	**MRSA**	Antibiotics
10	F	66	No	90	Screw fixation	3	No	Yes	Negative	Antibiotics
11	F	17	No	90	Locking plate	3	No	Yes	CoNS	Antibiotics
12	F	75	No	120	Percutaneus Fixation	5	Yes	Yes	*Staphylococcus aureus*	Antibiotics
13	F	75	No	45	Percutaneus Fixation	10	No	Yes	*Staphylococcus aureus*	Antibiotics
14	F	77	No	120	Locking plate	1	No	Yes	CoNS	Open debridment + plate remuval
15	M	77	No	155	Locking plate	7	No	Yes	CoNS + *Corynebacterium spp.*	Open debridment
16	F	78	No	85	Percutaneus Fixation	5	No	Yes	CoNS	Antibiotics
17	M	78	No	120	Screw fixation	6	No	Yes	CoNS	Antibiotics
18	F	81	No	70	Percutaneus Fixation	7	Yes	Yes	**MRSA** + CoNS	Antibiotics

Table II: risk factors

	Infection	No Infection	p
Continuos Variables	Average; SD		
AGE	62.6; 16	62.1; 16.2	0.89
Length of Surgery (Min)	**103.8; 44.5**	**89.2; 45.4**	**0,19**
Delay from trauma (days)	5.7; 5.5	6.2; 4	0,45
	Infection	No Infection	ODDS (p)
Dicotoums Variables			
Gender (Male)	3	134	0.45 (0,21)
Plate Fixation	7	190	0.8 (0.68)
Percutaneus Fixation	9	200	1.17 (0.74)
Other Techniques	2	44	1.1 (0.89)
Open reduction	13	293	1.25 (0.67)
Pre-operative lavage	**2**	**174**	**0.8 (0.026)**
First generation cephalosporin	**17**	**340**	**4.7 (0.13)**
Third generation cephalosporin	**1**	**82**	**0.25 (0.18)**
Other prophylaxis	0	12	0.91 (0.95)
Comorbidity	1	40	0.57 (0.6)
Concomitant fractures	1	23	1.05 (0.96)

Risk factors in bold had a p value less that 0.02 and were included in the logistic regression analysis.

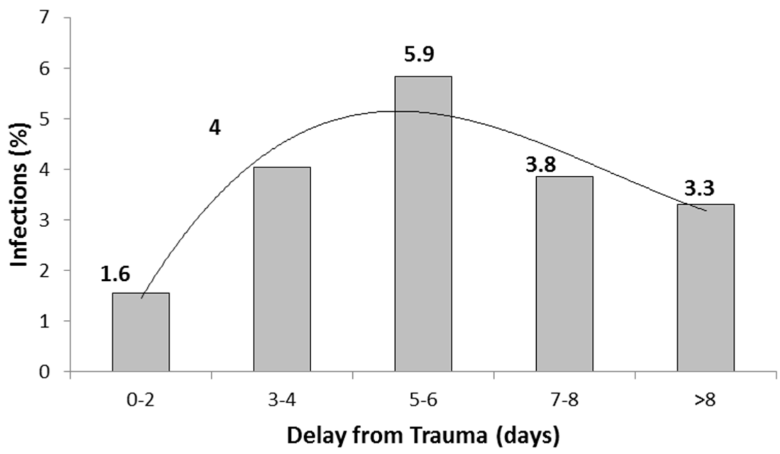
Table III: Logistic regression analysis

Variable	Odds ratio	95% CI	P
Pre-operative lavage	0,13	0,0292 to 0,5822	0,008
First generation cephalosporin	10,73	1,3151 to 87,6328	0,03
Length of surgery	1,009	0,9994 to 1,0197	0,05

Table IV Logistic regression (days 0-to-6)

Variables	**Odds ratio**	**95% CI**	**P**
Length of surgery	1,02	1,0026 to 1,0349	0,02
First generation cephalosporin	9,29	0,8943 to 96,4602	0,05
Pre-operative lavage	0,1	0,0109 to 0,8434	0,03
Delay to surgery	1,71	0,9679 to 3,0102	0,06

Figure 1



7
6
5
4
3
2
1
0
Infections (%)
1.6
4
5.9
3.8
3.3
0-2
3-4
5-6
7-8
>8
Delay from Trauma (days)