Approval number by the ethics committee: 207C041050020m/ceis/p.i./0348/2019

Protocol Title:

Application of antibiotic loaded calcium sulfate as prophylaxis for patients with risk factors for periprosthetic joint infections.

August 5th 2020, Tlalnepantla. Mexico

207c0401050020M/CEIS/P.I./0348/2019

Judgment

Tlalnepantla de Baz, Estado de México, May 13th 2019

MEETING MINUTE OF THE ETHICS COMMITTEE IN HEALTH RESEARCH OF THE HOSPITAL REGIONAL TLALNEPANTLA CORRESPONDING TO THE MONTH OF MAY 2019

M.D. JULIO CARLOS VELEZ DE LACHICA
Chief of Orthopedic surgery

On the present day after a careful review of the research protocol named: "Application of antibiotic loaded calcium sulfate as prophylaxis for patients with risk factors for periprosthetic joint infections.", the Ethics and Health Research Committee of hospital Regional Tlalnepantla ISSEMYM has **APPROVED** the research request presented by the principal investigator: Julio Carlos Velez de Lachica and co- investigators M.D. Juan Antonio Pages Ureña and M.D. Miguel Angel Ruiz Fragoso, since it complies with the bioethical principles of the hospital and is of great clinical relevance.

It is the responsibility of the principal investigator to notify the committee of any proposed changes regarding the work described within protocol.

M.D. Othón Romero Teran
Director of the Ethics and Health Research Committee

M.D. Jesus Reyes Reyes
Chief of Education and Research

M.D. Elizabeth Arizpe Graciela Amador
Vocal Secretary the Health Research and Ethics Committee

GOBIERNO DEL ESTADO DE MÉXICO ISSEMYM
TRAUMATOLOGÍA Y ORTOPEDIA
13 MAYO 2019
DR. JULIO [illegible] VÉLEZ DE LACHICA
CLAVE: 1650[illegible] CÉDULA: 548071
HOSPITAL REGIONAL TLALNEPANTLA

HOSPITAL REGIONAL TLALNEPANTLA
13 MAYO 2019
JEFATURA DE EDUCACIÓN E INVESTIGACIÓN MÉDICA

Title: Application of antibiotic loaded calcium sulfate as prophylaxis for patients with risk factors for periprosthetic joint infections.

INTRODUCTION

Total hip arthroplasty is one of the most widely recognized orthopedic surgeries in the world. Since its inception this technique has achieved remarkable success thanks to the excellent results in restoring function, eliminating pain, innovations in implant design, and improved quality of life. A devastating complications in this indication is peri-prosthetic infection.

There are many variables to consider when evalauting the risk of peri-prosthetic joint infection (PJI), including the types of implants, surgical technique, postoperative management and not least of all the patient. When assessing patients with hip and knee osteoarthritis or pertrochanteric fractures, socioeconomic status can introduce a significant risk of infection, that can be physically debilitating for the patient, challenging for clinicians and have an adverse economic impact for Health Institutes. (1)

In Mexico as in many developing countries, the necessary infrasctructure to provide widespread adequate healthcare is not available, but it is imperative to attempt to offer the best treatment available. This is how joint replacement, as a surgical technique, has to be approached daily in our institutions. In most cases comprehensive assessments of the patient are made, but despite this, there are chronic degenerative diseases, such as diabetes and obesity, that are difficult to control. These factors are not an impediment to contraindicate surgery, however they increase the risk of complications. Comorbidities like these are defined as non-modifiable risk factors of patients undergoing articular replacement surgery that increase the risk of infection rate. (2)

In order to reduce the risk of periprosthetic infection the application of local antibiotic at the surgical site, in addition to systemic antibiotics may be a promising concept. The local placement of antibiotics can result in high local concentrations, far higher than the levels that can be achived through systemic administration, the risk of elevated resulting systemic levels remains low (3)(4)(5). The reported use of local antibiotics at the surgical site range from direct placement of antibiotics at the surgical site(6)(7)(8)(9) to the combination of atibiotics with carrier materials in an attempt to prolong the level and duration of antibiotic(10)(11)(12). The use of calcium sulfate as a carrier for antibiotics has a history almost as long as that of antibiotics, with one of the first reported such uses dating back to 1953(13). Since this time, reports of the use of calcium sulfate in combination with amtibiotics in the treatment of osteomielitis have persisted (14–18) (19–23).

Modern commercially available formulations of calcium sulfate offer a versatility for mixing with a wide range of antibiotics (24), and in-vitro data indicates elevated antibiotic levels for up to 6 weeks (25), at levels that are capable of maintaining antimicrobial efficacy under conditions of high bacterial challenge (26–28). The application

of calcium sulfate has shown promising outcomes in peri-prosthetic joint revisión (29,30), but there is limited clinical data available regarding its use prophylactically.

The aim of this study was to evaluate local antibiotic loaded calcium sulfate as prophylaxis in patients undergoing hip and knee joint replacement with non-modifiable risk factors.

Economic Impact of Periprosthetic Infections

In 2012 in the United States, the annual cost in the treatment of patients with peri-prosthetic infection was analyzed, at 566 million Dollars, and it is expected to exceed 1.62 billion Dollars by 2020. It is expected that by the year 2020, the number of PJI cases for hip and knee is projected to be in excess of 65,000.(31)

The cost of secondary revision surgery to a peri-prosthetic infection is $60,000 Dollars higher than the revision surgery due to aseptic loosening. This increase is due to the longer hospital stay, prolonged antibiotic therapy, number of surgical interventions for remission of the infection, etc.(32) Likewise, an increase in the number of infections of surgical sites by methicillin-resistant organisms has been proven, increasing even more costs related to antibiotic therapy. (33)

In the United States, the cost of Hospitalization for peri-prosthetic infection is $107,264 Dollars; the cost for the treatment of infections was $110,459 Dollars per patient. The day of hospitalization is $3,473 Dollars and the cost of a revision arthroplasty is $36,607 Dollars. (32) At present in the United States, the increase in costs related to peri-prosthetic infections is surpassing the developments in prevention (34).

In 2018 in Mexico at the institutional level, the average hospitalization day was $7,757.00 Mexican pesos; the cost per surgical procedure was $ 21,004.00, a follow-up orthopedic clinical evaluation of $1,160.00; The cost of the revision implant reached $116,132.00 pesos. The average number of days of hospitalization for a patient with PJI was 60 days and the number of surgical procedures required varies with a minimum of 5. In this case, the cost of antibiotic therapy or the rest of the medications administered during their hospitalization it was not estimated. (35,36)

Several studies have shown that the identification of risk factors, decolonization and administration of prophylactic antibiotics leads to a substantial reduction of peri-prosthetic infections and with this, the cost involved in this condition. (32)

Diagnosis and Classifications:

<u>Current methods for the Diagnosis of peri-prosthetic infections.</u>

A gold standard has yet to be established for the diagnosis of peri-prosthetic infections, so the current diagnosis is based on a combination of clinical suspicion, serological studies, results in cultures, histology and molecular biology techniques.

Acute Phase Reactants:

The CRP rises after the arthroplasty procedure, in which its maximum peak is on the 2nd day and it can be normalized until 42 days postoperatively; however, after the 3rd day the CRP continues to increase and can be used as a marker for peri-prosthetic infection. In the same way, the ESR increases to its maximum peak on the 5th postoperative day and its values decrease to normal until 3 months (37–44)(45)

In this way, having the values of acute phase reactants that suggest a peri-prosthetic infection, we will be able to analyze the algorithm proposed by the American Academy of Orthopaedic Surgeons for the diagnosis of peri-prosthetic infections. In which the cut-off value for CRP is 93mg/L and for ESR of 44mm/hr. with an 88% risk of infection. If we find both reactants increased above this figure for more than 5 days after the arthroplasty, a culture of synovial fluid can be taken to assess the leukocytes which, with a value of 12,800 or more, have an 89% risk infection percentage. With both positive studies we can have the accurate diagnosis of peri-prosthetic infection in 100%. (46)

Classification:

Peri-prosthetic infections are classified according to the time of presentation of symptoms. The most recent classification stages infections in three areas: Early, acute hematogenous and chronic. Early infections are manifested during the first 3 months after surgery, the acute hematogenous infections with evolution of symptoms no greater than 3 weeks, and the chronic infections persist for more than 3 months and require a different treatment. When it comes to early and acute hematogenous infections, debridement and retention of the implant are still aceptable treatments. (47)

Biofilm in Prosthetic Implants

Although biomedical implants such as prosthetics have revolutionized medicine, they have also increased the risk of infections; in fact, it is considered that infections are the most frequent and severe complicataions.(48) Orthopaedic implant infections, especially prostheses, are particularly problematic since they remain in the body. Orthopaedic infections related to the implant are primarily caused by *Staphylococcus aureus* and secondly, by *Staphylococcus epidermidis*.(49)

In devascularized sites, implants act as a substrate for bacterial attachement and biofilm formation.(50,51). These biofilms require a large concentration of antibiotics for their elimination, typically at higher concentrations that can be achieved through systemic antibiotic administration (26). Debridement can physically removed most bacteria, but even with a thorough debridment technique some bacterial colonies can be established in poorly vascularized regions or on implants and result in infection recurrences. This is why it is not recommended to apply osteosynthesis and endoprosthesis in newly debrided tissue.

The mechanism of biofilm formation in smooth or coated implants has been broadly studied, determining the facilities that bacteria have for their adhesion in avascular implants

with porous coatings, and how difficult or impossible it is to eliminate them from these surfaces.(52)

Because antibiotic concentrations at sublethal doses cause persistence and resistance of the infection, the concentrations of the antibiotic to be administered as well as the method used must be taken into account. This is because infections in implants are located in avascular zones; therefore methods of antibiotic release at minimal inhibitory concentrations have been sought locally.

Antibiotic Release:

Polymethylmethacrylate (PMMA) has been used for many years as a local antibiotic release method, either in the form of spacers or in pre-filled beads.(10)**,**(53)

However, it has been shown that this method is not effective for the elimination of biofilm, since between 90 and 95% of the antibiotic remains trapped in the cement and only small amounts of antibiotic are released from the surface, releasing moderate concentrations. During the first hours after implantation, 90% of the pre-filled beads and 50% of the spacers are covered with biofilms at the time of extraction associated with the induction of bacterial resistance by their limited antibiotic concentration.(23–26). Small colony variants (SCV) require up to 100 times more than minimal inhibitory concentrations and for pathogens embedded in the biofilm, up to 1000 times the minimum inhibitory concentrations (MIC) for their elimination. This suggests that neither the systemic antibiotic therapy nor the antibiotics released by PMMA are useful for the elimination of the biofilm. (54,55)

In order to eliminate the residual biofilm, local antibiotic release is required to provide high concentrations of antibiotic for prolonged periods of time. Most of the related pathogens in bone infections are Gram-positive susceptible to Vancomycin; most of the Gram negative are susceptible to tobramycin, showing less cytotoxicity and adverse effects. (56)

Risk Factors

It has been proven that the non-modifiable risk factors of patients undergoing Articular Replacement Surgery increase the risk of infection rate. According to a meta-analysis based on 14 studies from January 1980 to March 2014, the following were identified as risk factors for developing a peri-prosthetic infection: Body mass index, Diabetes Mellitus, corticosteroid therapy, hypoalbuminemia, rheumatoid arthritis, blood transfusion, presence of secretion in any wound, wound dehiscence, superficial infection in surgical site, coagulopathy, immunodeficiency, history of nosocomial infection, prolonged surgery time and previous surgery of the region. (57)

	Risk Factors	Characteristics
1	Body Mass Index	>40 kg/m2
2	Wound Drain, dehiscence or another surgical active infection	Any active wound that is draining before the joint replacement
3	History of Nosocomial Infection	Any infection acquired in the Hospital
4	Prolonged surgical time	Greater than 120 minutes and every 15 minutes of extra surgery increases a 9% risk of infection.
5	Decompensated Type 2 Diabetes Mellitus	HbA1C > 7
6	Serum albumin	< 3.4 g/dl
7	Rheumatoid Arthritis	In treatment or not.
8	Blood transfusion Transoperative Bleeding	During the 24 hours after surgery. Greater than 1000cc
9	History of Prosthetic Surgery	Prosthetic Revision Surgery or history of a knee or hip primary prosthetic surgery
10	Immunosuppression	Lymphocytes < 1,500
11	Malignancy	History of any malignant tumor.
12	Corticosteroid Therapy	>1 month of continuous treatment

Table 1. Main non-modifiable risk factors for periprosthetic joint infections.

There are other risk factors such as: age over 65 years, kidney failure, liver failure, smoking, drug and alcohol abuse, prolonged drainage, etc.; however, the fact that they are representative for an infection has not been corroborated. (58,59)

Although there are multiple studies on periprosthetic infections, there is still no one that proves the percentage represented by each risk factor; however, it has been corroborated that these comorbidities have a significant risk factor for periprosthetic infections. (1)

Calcium Sulfate Vs. PMMA

Polymethyl methacrylate (PMMA) loaded with antibiotic has been used for a long time as a carrier and release method, either as a spacer or as beads, increasing the local levels of antibiotic in the surgical site. However, its limited clinical benefit has been proven. Once the antibiotics have been released from the nonabsorbable layer of cement, it becomes a foreign body susceptible to bacterial colonization and biofilm formation, which is why it is essential to perform a new surgical procedure for its extraction.(60–62). PMMA has a high setting temperatura wich means that thermosensitive antibiotics cannot be combined with it.

Calcium sulphate as a vehicle for antibiotic release is completely absorbed within 4 to 8 weeks, completely releasing the full antibiotic load. Due to its low setting temperature, it has the potential to be mixed with thermosensitive antibiotic. As it is fully absorbed there is no residual material that can act as nidus for bacterial attachment and biofilm formation. Clacium sulfate also presents a minimal risk to damage components of joint prosthesis when implanted into or adjacent to the articulating surfaces. In contrast, PMMA is designed as a cement for prosthetic implantation and this characteristics can be impaired by its combination with high quantities of antibiotic, pontentially leading to early loosening.

Calcium Sulphate Vs. PMMA Comparison		
Features	**Calcium Sulfates**	**PMMA**
Gradual release of the antibiotic	YES	NO
Total release of the antibiotic	YES	NO
Nidus for bacterial attachment	NO	YES
Requires its Extraction	NO	YES
Works with heat-sensitive antibiotics	YES	NO
Serves as a spacer	NO	YES
Effective for dead space management	YES	YES

Table 2. Correlation between antibiotic loaded Calcium Sulfate versus PMMA.

RESEARCH QUESTION

Is there a difference in the incidence of periprosthetic infection in patients with risk factors and the application of prophylactic antibiotic loaded calcium sulfate versus patients with risk factors without prophylactic treatment?

HYPOTHESIS

H_0 . There is no significant difference in the incidence of periprosthetic joint infection between patients who received local prophylaxis versus conventional prophylaxis.

H_1.- The incidence of periprosthetic infection in patients with non-modifiable risk factors and prophylactic application of antibiotic loaded calcium sulfate is lower than in patients without prophylactic treatment with calcium sulfate.

JUSTIFICATION

Medical Justification

Peri-prosthetic infections, although rare, are devastating. They can occur at any time after the surgical treatment; however, most are diagnosed within the first 2 years after the surgical treatment. Once an infection occurs, the mortality in the person suffering from it increases from 2.7 to 18%, this far exceeds the mortality rate that occurs in patients who undergo a revision arthroplasty.

A peri-prosthetic infection is not only overhelming for patients and doctors, but also health institutions. When a patient becomes infected, treatment costs are usually 4 times more expensive than the costs generated in the initial procedure.

If a peri-prosthetic infection causes so much damage, it would be prudent to take action to prevent it. The truth is that there are various strategies developed by different national and international agencies to prevent and treat infections, and yet there are still cases of infection.

Social Justification

Peri-prosthetic infection has an incidence in the United States of America of 0.69% and 1.09% for total hip arthroplasty (THA) and 0.74% and 1.38% for total knee arthroplasty (TKA), respectively. The projection for the future is for these figures to increase, which would mean that the health system could be significantly affected. There is also a relationship between peri-prosthetic infections and mortality.(63)

The Institute of Social Security for the State of Mexico and Municipalities (ISSEMyM, as in Spanish), is an institute that has a large population of beneficiaries with a diagnosis of osteoarthritis and hip fracture, and many of these patients will undergo articular replacement surgery. The purpose of this study is that these patients do not suffer from a peri-prosthetic infection, and therefore, avoid not only the human suffering, but the high expense that is generated when treating this pathology.

OBJECTIVES

General Objective:

To compare the incidence of early periprosthetic infection in patients with non modifiable risk factors and prophylactic antibiotic loaded calcium sulphate ("Study" group) versus patients without antibiotic loaded calcium sulphate ("Control" group).

Specific Objectives:

- To know the incidence of early periprosthetic infection in patients with non-modifiable risk factors to present infection.

- To create a Control Group and an Study Group for the application of antibiotic loaded calcium sulphate as a prophylactic treatment in patients with non-modifiable risk factors for peroposthetic infection.
periprosthetic infection.

- To perform statistical analysis for the control group and the experimental group.

Secondary objectives:

- Establish differences in the cost benefit of prophylaxis with or without antibiotic loaded calcium sulphate beads by length of hospital stay.

PARTICIPANTS ELIGIBILITY CRITERIA

Inclusion Criteria:

- All patients who come to the Tlalnepantla Regional Hospital with hip or knee osteoarthritis and hip fracture that requieres joint replacement.
- All patients who have any of the Non-Modifiable Risk Factors prior to surgery or during transoperative period. (Table 1)
- Patients entitled to the ISSEMyM
- Patients over 60 years old (64)
- Patients with a cardiopulmonary assessment prior to their surgical treatment
- Patients who undergo primary non-cemented Hip and Cemented Knee Joint Replacement.
- Patients who do not have an active system infection.

Exclusion Criteria:

- Patients who are not beneficiaries of the ISSEMyM
- Patients who do not have the diagnosis of Hip or knee osteoarthritis
- Patients under 60 years old (64)
- Patients with hip fractures that requires an internal fixation.
- Patients with active systemic infection
- Patients with Renal or Hepatic Insufficiency
- Patients who do not have any of the risk factors for periprosthetic infection. (Table 1)

Elimination Criteria:

- Patients that lose their validity of institutional rights and do not follow up the treatment.
- Patients who die during the study due to other causes not related to the orthopedic procedure.
- Patients who for any reason do not give continuity to the treatment or do not follow medical indications.

METHODS AND PATIENTS

Study Design

This was a prospective, longitudinal and randomized controlled trial. The study was performed at the department of Orthopedics at The *Hospital Regional Tlalnepantla* (Mexico) and approved by the ethics and research committee.

The eligibility criteria for this study were: being over 60 years of age, having one or more non-modifiable risk factors, patients who underwent for total hip or knee joint replacement between June 2019 and May 2020. The exclusion criteria taken into consideration were: Patients with an active systemic infection, kidney or liver failure, known allergies to vancomycin or cephalosporins. All patients who met the selection criteria were invited to be part of the study, detailing that they could have a systemic or local prophylactic therapy according to the group assigned to the roasting. Those who accepted signed a letter of informed consent agreeing to join the study. Apendix 1

Patients were randomized with the *randomizer app v0.2.6-beta* and assigned into one of both control or study group.

Subjects enrolled in the control group received a prophylactic dose of 750 mgs of cetriaxone 20 minutes before joint replacement surgery and every 8 hours for 24 hours. Regarding the patients assigned to the study group, none received parenteral antibiotic prophylaxis. At the operating room and before the final implantation of the prosthesis, the purified calcium sulfate beds impregnated with 3g of vancomycin were applied locally. For the local prophylaxis it was used: Stimulan Kit (Biocomposites Ltd, United Kingdom) which includes 10 cc (20 g) of calcium sulphate hemihydrate powder, a pre-mixing solution bulb, mould of 3, 4.8 and 6 mm sizes of beads and spatula. 3g of vancomycin powder was mixed with each 10 cc of calcium sulphate in the mixing bowl, after 30 seconds the resulting paste was applied to the moulds using the spatula and allowed to set for 10 to 15 minutes. In hip joints the 3 mm beads were applied and pulverized on the previosly reamed acetabular cavity. For the proximal femur, the pearls were inserted into the canal and the final components were placed by impactation, ending the pulverization of the beads in the interface areas. The remaining beads were applied to the soft tissue around the prosthesis. Instead for the knee joint, the 4.8mm beads were applied inside the femoral and tibial canal, the remaining beads were placed into the soft tissue around the prosthesis. Antibiotic-loaded polymethylmethacrylate cement was not used in any subject.

After surgery, CRP and ERS biomarkers were analyzed at day 5 and weeks 4, 8, and 12 to determine acute periprosthetic infection. A CRP > 93mg/L and ERS >44mm/h were the cutoff value for infection risk. If CRP were elevated alone or with ESR, then the synovial fluid were obtain and analyzed. A threshold of Leucocytes > 12,800 cells/μL and/or positive culture was defined as acute periprosthetic joint infection. The information obtained from patients is noted on the data collection sheet. Apendix 2 and 3

The primary outcome of this study was to determine the relationship between prophylaxis with local calcium sulfate beads in patients with non-modifiable risk factors for PJI and its evolution without infection compared with a control group. The secondary

outcome was to know the institutional economic cost according to the length of hospital stay.

Prospectively recorder data included: patient demographics; biomarkers values before and after surgery, diagnosis and if it was knee or hip replacement, risk factor for PJI, Synovial fluid analysis, length of hospital stay, and the need for periprosthetic joint infection treatment.

Statistical Analysis.

According to our biostatistics department and the sample size determination estimated by STATS 2.0 Software, this trial requiered enrollment of 76 patients to obtain a statistically valid meaningful.

The presence of periprosthetic infection in both groups was evaluated by chi-square and Lambda tests for dichotomous nominal and qualitative variables with longitudinal direction and relative risk test. Demographic variables were tested by central trend measures, t-student for independiente continuous variables and chi-square for categorical variables. Statical analysis was performed using SPSS Statistics 26 IBM software. A p value <0.05 was considered to reject the null hypothesis.

Results.

Eigthy seven subjects were enrolled to the study in the period between June 2019 to May 2020, Four of them were excluded (all 4 patients lost institutional validity so postopertive follow-up was no obtain). A total of 83 patients were evaluated, for the female we obtained 44 cases (53%) and for male 39 cases (46.9%). We randomly assigned subjects in two groups for the longitudinal design study. All the patients had at least one of the main risk factors for presenting periprosthetic infection. Forty subjects (48%) were enrolled for the control group and received conventional intravenous prohpylactic antibiotic therapy for a total of 24 hours. For the study group 43 patients (51.8%) received local antibiotic therapy with calcium sulfate beads mixed with vancomycin during the surgery. An average age of 77.3 years was found for the control group (61 to 90 years) versus 75.9 (62 to 89) years in the study group. BMI was the main risk factor found for both groups (16 patients 19.28%) follow by the decompensated type 2 diabetes (15 patients 18.07%). Both knee and hip prostheses were applied. A total of 38 knees (52.5% for control group versus 39.5% for the study group) and 45 hips were treated (47.5% and 60.5% for control and study groups respectively). There was no difference in demographic variables for both groups $p>0.05$.

Although the prophylactic treatment was applied in both groups, the presence of early periprosthetic infection was found in 37.3%. In 31 subjects enrolled to the control group, 67.5% developed acute PJI, while the study group had 9.3%. Variable analysis identified that local prophylaxis with calcium sulfate beads compared to conventional prophylaxis, can further prevent the presence of acute knee or hip periprosthetic infection in patients with non-modifiable risk factors ($p=0.022$) with a 0.13 of relative risk . Lenght of stay was also shorter in the study group at 4.6 days (range: 2-23 days) compared to 15.25 days in the control group (range: 2-32 days; $p<0.001$).

DISCUSSION

Our Health Mexico Institute, it's a representation of most hospitals in developing conuntries. In wich up to 800 patients a week, are attend for external consultation in the Orthopedic's department. This is not exclusive to orthopedic services; as most of other specializations are over saturated. This problem is the result of lack of adequate management and control over chronic degenerative disorders. In this way, it has been observed that a high number of patients that have had joint replacement surgery but do not have an adecuate control of their chronic conditions, have .an increase risk of ingfection. This is due to risk factors that can not be measured, in the short or médium term. Despite all this; in many cases joint replacement surgery is needed, in order to give the patient a better quality of life. It has been demostrated that there's an increase risk of infection in patients with unmodifiable risk factors(65–67)(68). Once the infection has been diagnosed, the treatment that follows is complex and not without complications; in patients who also have risk factor or comorbidities, the treatment becomes even more difficult and expensive.

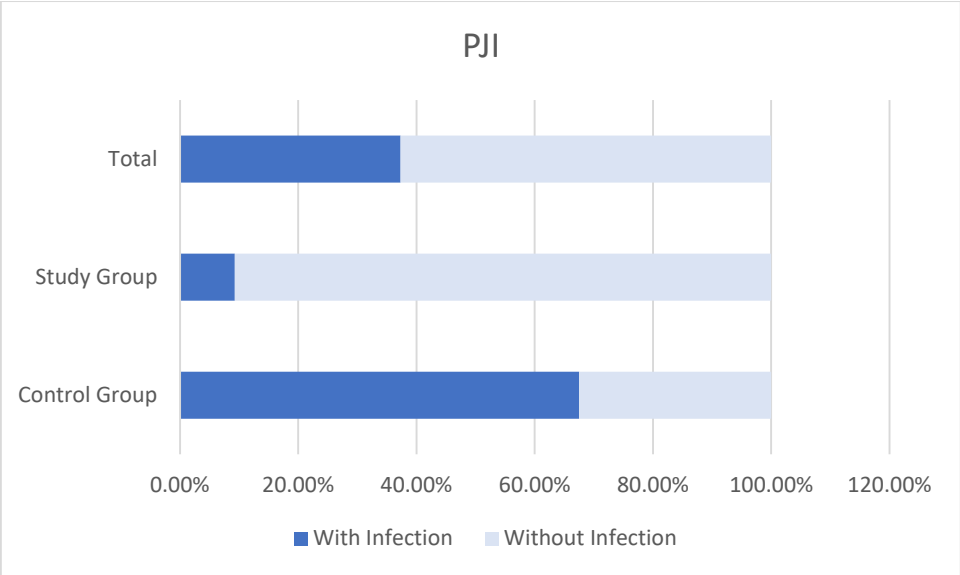
In this study we have found that the local antibiotic prophylaxis can influence to a greater degree in the prevention of periprosthetic infections, mainly in patients with non modifiable high risk factors sucha as: high body mass index (BMI); as well as lack of metabolic control of type 2 diabetes.(69–71) The application of local antibiotics has been studied in several occasions, yet the direct application of bone prosthesis interphase hasn't been well established. In this study however, we have managed to identified benefitial results in the application of local antibiotics in relation to the prosthesis components and the surrounded tissue.

Periprosthetic infections continue to be a problem with devastating consequences for the surgeon, the patient and the health system. Based in our study, medicated calcium sulfate beads as a local release method of prophylactic antibiotic therapy, represents a possibility in the reduction of 86.6% the presence of periprostethic infections in patients with non-modifiable risk factors and their association with complications and economic cost. Unfortunately, this study was based on patients with the presence of acute periprosthetic infection, and there are no long-term results yet. However, it would be expected to have similar results. Likewise it was performed both in knee and hip prosthesis, so a deeper study is required for each type of prosthesis and each risk factor.

Conclusions

Medicated calcium sulfate beads as a local antibiotic prophylaxis method in patinets with non-modibiable risk factors undergoing hip or knee replacement adds adecuate protection, reducing the risk of developing acute preiposthetic joint infection. However, more studies are required to corroborate these results in a long term basis.

GRAPHS AND TABLES



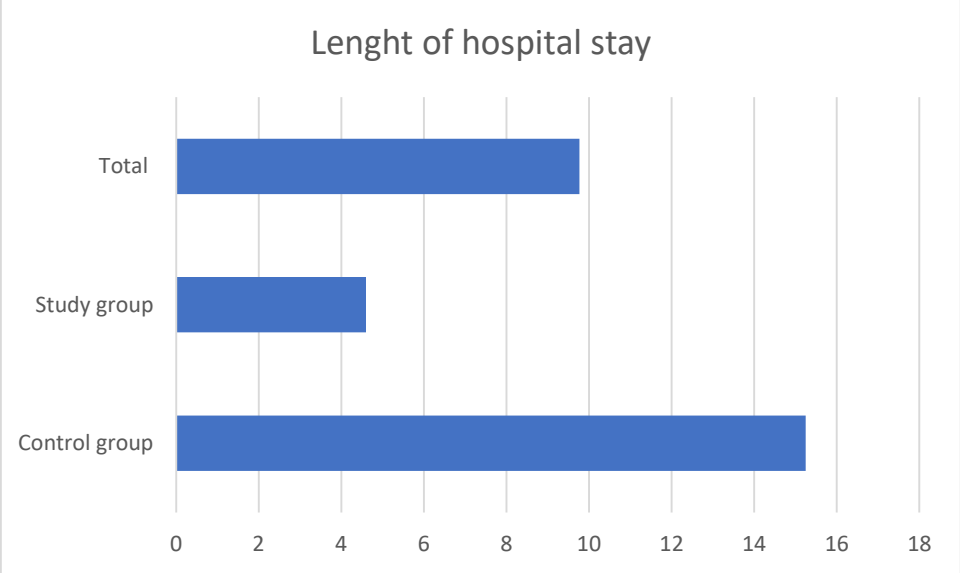


Table 3. Outcomes and P Value for non modifiable risk factors associated with PJI

Variable/Groups	Control group n=40		Study n=43		Total n=83/ 100%		p Value
Age	77.3 years (61-90)		75.9 years (62-89)		76.6 years +/- 8.5		0.2
Gender							0.721
Male	18 (45%)		21 (48.8%)		39 (46.9%)		
Female	22 (55%)		22 (51.2%)		44 (53%)		
Non modifiable risk factors		%		%		%	0.427
BMI	6	15	10	23.26	16	19.28	
Wound Drain, dehiscence or surgical activ	4	10	2	4.65	6	7.23	
History of nosocomial infection	3	7.5	3	6.98	6	7.23	
Prolonged surgical time	4	10	3	6.98	7	8.43	
Decompensated Type 2 Diabetes Mellitus	7	17.5	8	18.60	15	18.07	
Serum Albumin	4	10	1	2.33	5	6.02	
Rheumatoid Arthritis	5	12.5	2	4.65	7	8.43	
Blood transfusion Transoperative Bleeding	5	12.5	7	16.28	12	14.46	
History of prosthetic surgery	1	2.5	3	6.98	4	4.82	
Immunosuppression	1	2.5	0	0.00	1	1.20	
Malignancy	0	0	3	6.98	3	3.61	
Corticosteroid Therapy	0	0	1	2.33	1	1.20	
Joint Prosthesis							0.236
Knee	21 (52.5%)		17 (39.5%)		38 (45.7%)		
Hip	19 (47.5%)		26 (60.5%)		45 (54.3%)		
Lenght of hospital stay	15.25 days (2-32 days)		4.6 days (2-23)		9.77 days +/- 9.37		<0.001
Periprosthetic Joint Infection							0.022
With Infection	27 (67.5%)		4 (9.3%)		31 (37.3%)		
Without Infection	13 (32.5%)		39 (90.7%)		52 (62.7%)		

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Appendix 1

INFORMED CONSENT FORM

HOSPITAL REGIONAL TLALNEPANTLA ISSEMYM
Place: TLALNEPANTLA ESTADO DE MEXICO
Date:
Name:

According to the Official Mexican Law NOM-004-SSA3-2012, of the medical clinical file, published in the Official Gazette of the Federation, this written and signed document is presented by the patient and / or legal representative, by means of which he accepts, under due information, the risks and benefits expected.

As a patient I agree to participate in the research protocol entitled: Application of antibiotic loaded in calcium sulfate beads as prophylaxis of patients with risk factors for peri-prosthetic infection. Where I am explained possibility of being randomized in the study group, calcium sulfate loaded with 3 gr of vancomycin will be applied during the prosthetic application as the interface between the acetabulum and the metal cup and between the femoral canal and the porous stem in the hip replacement, for the articulation of the knee, calcium sulfate will be applied in the femoral and tibial canal and in the soft ridged tissue. For the control group, the use of 1 gr of ceftriaxone 30 minutes before surgery is used as a protocol for antibiotic prophylaxis. I DECLARE: 1.- That I have received the invitation to participate as a research subject without having been subjected to inappropriate influences or intimidation. 2.- I know the reasons why I was elected, that my participation is voluntary and that I have the freedom to refuse and withdraw at any time without any penalty. 3.- that the purpose of the project has been explained to me and that I have enough information about the risks and benefits during my procedure. 4.- I have understood the possibility of anaphylaxis to the medication, risk of peri-prosthetic infection, and that I may require complementary treatments due to problems inherent to the medical practice, as well as the reasonable benefits that can be expected. 5.- I can access information about the results obtained during the study and that I will not receive any remuneration for participating in this study other than the reasonable benefits explained from the handling. 6.- The responsible researcher has explained to me that I will not be identified in the presentations or publications that derive from this study and that the data related to my privacy will be handled confidentially.

Agree

_____

NAME AND SIGNATURE

_____

FIRST WITNESS NAME AND SIGNATURE

_____

SECOND WITNESS NAME AND SIGNATURE

Apendix 2

Name	
ISSEMyM ID:	
Age:	
Surgery Date	
Diagnosis	
Treatment	
Another diagnosis	

Random group					
Risk Factors					
CRP	Preop	5 days	4 weeks	8 weeks	12 weeks
ESR	Preop	5 days	4 weeks	8 weeks	12 weeks
Leucocytes in sinovial fluid					
Tissue or sinovial fluid culture					
Periprosthetic joint infection (Yes/No)					

Apendix 3

Economics

	Study	Control
Time in surgery room		
Lenght of hospital stay in days		