Protocol Title:

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

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

PRESENTS:

Principal Investigator
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ORTHOPAEDIC SURGEON

Sub-Investigators
M.D. JUAN ANTONIO PAGÈS UREÑA
M.D. MIGUEL ANGEL RUIZ FRAGOSO

ESTADO DE MEXICO, MEXICO  May, 22 of 2019
Title: Application of antibiotic loaded calcium sulfate as prophylaxis for patients with risk factors for periprosthetic joint infections.

Total joint 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 evaluating 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.  

In Mexico as in many developing countries, the necessary infrastructure 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.  

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 achieved through systemic administration, the risk of elevated resulting systemic levels remains low. 3-5 The reported use of local antibiotics at the surgical site range from direct placement of antibiotics at the surgical site 6-9 to the combination of antibiotics with carrier materials in an attempt to prolong the level and duration of antibiotic 10-12. 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 antibiotics in the treatment of osteomielitis have persisted 14-23.

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 revision 29-30, but there is limited clinical data available regarding its use prophylactically.
The aim of this study is to evaluate antibiotic loaded calcium sulfate as prophylaxis in patients undergoing hip 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 periprosthetic 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:**

Current methods for the Diagnosis of peri-prosthetic infections.

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.\(^{37-45}\)

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 acceptable 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 complications.\(^{65}\) 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*.\(^{64}\)

In devascularized sites, implants act as a substrate for bacterial attachment and biofilm formation.\(^{48,49}\) 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.\(^{50}\)

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. 10,51

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. 23,24, 25, 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. 56-57

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. 58

**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. 59
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index</td>
<td>&gt;40 kg/m²</td>
</tr>
<tr>
<td>Corticosteroid Therapy</td>
<td>&gt;1 month of continuous treatment</td>
</tr>
<tr>
<td>Wound Drain</td>
<td>Any wound that is draining</td>
</tr>
<tr>
<td>Wound Dehiscence</td>
<td>Any unhealed wound</td>
</tr>
<tr>
<td>Surgical wound surface infection</td>
<td>Infected surgical wound around the surgical site of the arthroplasty</td>
</tr>
<tr>
<td>History of Nosocomial Infection</td>
<td>Any infection acquired in the Hospital</td>
</tr>
<tr>
<td>Prolonged surgical time</td>
<td>Greater than 120 minutes and every 15 minutes of extra surgery increases a 9% risk of infection.</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>HbA1C &gt; 7</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&lt; 3.4 g/dl</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>In treatment or not.</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>During the 24 hours after surgery.</td>
</tr>
<tr>
<td>Transoperative Bleeding</td>
<td>Greater than 1000cc</td>
</tr>
<tr>
<td>History of Prosthetic Surgery</td>
<td>Prosthetic Revision Surgery</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Lymphocytes &lt; 1,500</td>
</tr>
<tr>
<td>Malignancy</td>
<td>History of any malignant tumor.</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Any type of coagulopathy</td>
</tr>
</tbody>
</table>

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.  

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.  

CALCIUM SULFATE VS. PMMA  

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. 53, 62, 63. PMMA has a high setting temperature which 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. Calcium 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 characteristic can be impaired by its combination with high quantities of antibiotic, potentially leading to early loosening.

<table>
<thead>
<tr>
<th>Calcium Sulphate Vs. PMMA Comparison</th>
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<tbody>
<tr>
<td>Gradual release of the antibiotic</td>
</tr>
<tr>
<td>Total release of the antibiotic</td>
</tr>
<tr>
<td>Nidus for bacterial attachment</td>
</tr>
<tr>
<td>Requires its Extraction</td>
</tr>
<tr>
<td>Works with heat-sensitive Antibiotics</td>
</tr>
<tr>
<td>Serves as a spacer</td>
</tr>
<tr>
<td>Effective for dead space management</td>
</tr>
</tbody>
</table>

Table 2.

**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**

The incidence of periprosthetic infection in patients with 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 overwhelming 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.

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 arthrosis 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.

General Objective:

To compare the incidence of early periprosthetic infection in patients with high risk factors and prophylactic antibiotic loaded calcium sulfate (“Experimental” group) versus patients without antibiotic loaded calcium sulfate (“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 Experimental Group for the application of antibiotic loaded calcium sulphate as a prophylactic treatment in patients with non-modifiable risk factors for 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 spheres of calcium sulfate.

**Study Design:**

Experimental Prospective Longitudinal

**Study Site**

According to the data reported by the Biostatistics service of the Tlalnepantla Regional Hospital, the number of Hip and Knee Joint Replacement Surgeries performed in year 2017 from January to December was 94 procedures.

The *Decision Analyst STATS 2.0* application was used to calculate the sample number taking as a whole the 94 joint replacement procedures performed for one year. A statistically significant number of 76 patients for our environment was obtained.

**Inclusion Criteria:**

- All patients who come to the Tlalnepantla Regional Hospital with hip or knee osteoarthritis and hip fracture that requires 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 67
- 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 67
- 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.

Material and Methods:

Analysis of the incidence of periprosthetic infection

All patients who have one or more risk factors, that require treatment by primary hip and knee joint replacement will be included. It will be explained to the patients that two groups will be applied: control and experimental, in which they will be randomly allocated in the study. In the study group, calcium sulphate loaded with vancomycin will be applied during the prosthetic application as an interface between the acetabulum and the metal cup and between the femoral canal and the porous stem in the hip replacement, for the knee joint the calcium sulphate will be applied into femoral and tibial canal and sorrounded sof tissue.

CRP and ESR prior to the surgical event will be requested as the patient's reference value. Subsequently, ESR and CRP will be evaluated within the first 5 days after surgery and subsequently, within 4, 6, 8 and 12 weeks. If during these gatherings the CRP > 93 mgs/dl and ESR 44 mm/hr, they will undergo aspiration of joint fluid. If leukocytes are > 1200, the diagnosis of Acute Periprosthetic Infection will be obtained.

Statistical Analysis Plan

The results of ESR, CRP as well as the presence of risk factors and the prevalence of infection will be collected in a data sheet (appendix 2). Once all the results have been obtained, a statistical analysis will be carried out using T student and mesure of central tendency statistics. To evaluate the risk factors related to infection, will be use logistic regression analysis.

Health Economic analysis

The study will also evaluate any health economic benefits of the experimental group compared to the control group. To do so, the following information will be collected for each patient in the study: (Appendix 3)

- Time in operating room
- Length of hospital stay
- Clinical follow-up (scheduled)
- Infection following treatment (yes/no)
- Additional surgery (for same original condition)
- Amount of antibiotic therapy during stay.
The control group will be analyzed and compared with the experimental group for differences in the above criteria. Statistical analysis of both groups will be carried out. Any statistically meaningful differences will be used to calculate potential health economic benefits of the experimental group, based upon information on standard costs for time in the operating theatre, hospital stay, and outpatient visits, and additional procedures.

Schedule of Activities

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<td>Submitting research protocol to ethics committee.</td>
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<td>Creation of Control and Experimental Group</td>
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<tr>
<td>Including patients randomly to groups</td>
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<tr>
<td>Collecting Data</td>
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<tr>
<td>Obtaining Results and Statistical Analysis</td>
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<tr>
<td>Conclusions</td>
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Bibliography:


35. Official diary. First section 21. AGREEMENT ACDO.AS3.HCT.291117 / 275.PDF and its Annexes, issued by the H. Technical Council in the ordinary session held on November 29, two thousand and seventeen, regarding the approval of the Unit Costs by Level of Medical Care. 2018.


Appendix 1

Informed Consent Sheet investigation.

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
Appendix 2

<table>
<thead>
<tr>
<th>Name:</th>
<th>ISSEMyM ID:</th>
<th>Age:</th>
<th>Date of Surgery:</th>
<th>Diagnosis:</th>
<th>Treatment:</th>
<th>Other diagnosis:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group by Random Risk Factor(s)</th>
<th>CRP</th>
<th>Preop</th>
<th>5 days</th>
<th>4 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>Preop</td>
<td>5 days</td>
<td>4 weeks</td>
<td>6 weeks</td>
<td>8 weeks</td>
<td>12 weeks</td>
<td></td>
</tr>
<tr>
<td>Leucocytes in sinovial fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Periprosthetic Joint Infection (Yes/No)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
Appendix 3

Economic data sheet.

<table>
<thead>
<tr>
<th>Time in operating room</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Clinical follow-up, and</td>
<td></td>
</tr>
<tr>
<td>Infection following treatment</td>
<td></td>
</tr>
<tr>
<td>Additional surgery</td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td></td>
</tr>
</tbody>
</table>
Protocol Title:

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

INFORMED CONSENT FORM AND COMMITTEE APPROVAL

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

PRESENTS:

Principal Investigator

M.D. JULIO CARLOS VELEZ DE LACHICA

ORTHOPAEDIC SURGEON

Sub-Investigators

M.D. JUAN ANTONIO PAGÈS UREÑA

M.D. MIGUEL ANGEL RUIZ FRAGOSO

ESTADO DE MEXICO, MEXICO  May, 22 of 2019
Informed Consent Sheet investigation.
HOSPITAL REGIONAL TLALNEPANTLA ISSEMYM
Place: TLALNEPANTLA ESTADO DE MEXICO
Date:
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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.

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Agree

______________________________
NAME AND SIGNATURE

______________________________
FIRST WITNESS NAME AND SIGNATURE

______________________________
SECOND WITNESS NAME AND SIGNATURE
Tlalnepantla de Baz. Estado de México, 13 de mayo de 2019.

M. E. JULIO CARLOS VÉLEZ DE LACHICA.
ADSCRITO AL SERVICIO DE ORTOPEDIA Y TRAUMATOLOGÍA
PRESENTE:

Por éste medio reciba un cordial saludo, así mismo, adjunto al presente Acta del Protocolo de Investigación presentado en la Sesión ordinaria del Comité de Ética en Investigación en Salud, el día 27 de mayo de 2019, de éste Hospital Regional de Tlalnepantla, titulado:

"APLICACIÓN DE ANTIBIÓTICO CARGADO EN PERLAS DE SULFATO DE CALCIO COMO PROFILAXIS DE PACIENTES CON FACTORES DE RIESGO PARA INFECCIÓN PERI-PROTESICA."

Sin más por el momento, quedo de usted.

ATENTAMENTE

DR. JESÚS REYES REYES.
JEFE DE LA UNIDAD DE EDUCACIÓN E INVESTIGACIÓN MÉDICA.

c.c.p. Archivo
JRR/mtia.
Reunidos en la sala de juntas del área de Enseñanza, los integrantes del Comité: revisaron el Protocolo Investigación que presentan el M. E. Julio Carlos Vélez de Lachica, médico adscrito de la especialidad de Traumatología y Ortopedia Autor de la Investigación y los coautores médicos residentes Juan Antonio Pages Ureña y Miguel Angel Ruiz Fragozo de este Hospital Regional de Tlalnepantla, titulado:

“APLICACIÓN DE ANTIBIÓTICO CARGADO EN PERLAS DE SULFATO DE CALCIO COMO PROFILAXIS DE PACIENTES CON FACTORES DE RIESGO PARA INFECCIÓN PERI-PROTESICA.”

Con el siguiente resultado:

Se aprueba la realización del Protocolo de Investigación presentado, ya que cumple con los principios y valores bioéticos de: beneficencia, respeto a las personas y equidad.

Siendo las 12:00 horas del día 13 de mayo de 2019, se declara concluida la reunión del Comité, firmando los que participaron en la misma.

E. en C. Ped. Othon Romero Tarán
Presidente del Comité de Investigación en Salud y del Comité de Ética e Investigación en Salud

E. en Ortopedia Julio Carlos Vélez de Lachica
Titular de la Especialidad
Director de Investigación

E. en NC. Jesús Reyes Reyes.
Jefe de la Unidad de Educación e Investigación Médica

E. en Anest. Norma Teresa Magaña Acosta
Vocal Secretario del Comité de Investigación en Salud y del Comité de Ética e Investigación en Salud
Sesson of the ethics and health research committee of the Tlalnepantla Regional Hospital
for the month of May 2019

M.D. JULIO CARLOS VELEZ DE LA CHICA
Chief of Orthopedic surgery.
On 13/5/2019, after review of your Investigation protocol of: "Application of antibiotic loaded calcium sulfate as prophylaxis for patients with risk factors for periprosthetic joint infections." The investigational ethical board and the education area of Hospital regional tlanepantla ISSEMYM, has APPROVED your request of the investigation, presented by the principal investigator: Julio Carlos Velez de Lachica and co-investigator M.D Juan Antonio Pages Ureña, MD Miguel Angel Ruiz Fragoso, since it complies with the bioethical principles and being of great clinical relevance.

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

M. E. Othon Romero Teran
Director of Investigation board.

M.E. Jesus Reyes Reyes
Chief of Education Division

INSTITUTO DE SEGURIDAD SOCIAL DEL ESTADO DE MÉXICO Y MUNICIPIO
Av. Miguel Hidalgo pte. núm. 600, col. La Merced, C.P. 50080, Toluca, Estado de México.
Tel.: (01 722) 226 19 00.
Protocol Title:

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

STATISTICS ANALYSIS PLAN

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

PRESENTS:

Principal Investigator

M.D. JULIO CARLOS VELEZ DE LACHICA

ORTHOPAEDIC SURGEON

Sub-Investigators

M.D. JUAN ANTONIO PAGÈS UREÑA

M.D. MIGUEL ANGEL RUIZ FRAGOSO

ESTADO DE MEXICO, MEXICO May, 22 of 2019
Analysis of the incidence of periprosthetic infection

All patients who have one or more risk factors Table1, that require treatment by primary hip and knee joint replacement will be included. It will be explained to the patients that two groups will be applied: control and experimental, in which they will be randomly allocated in the study. In the study group, calcium sulphate loaded with vancomycin will be applied during the prosthetic application as an interface between the acetabulum and the metal cup and between the femoral canal and the porous stem in the hip replacement, for the knee joint the calcium sulphate will be applied into femoral and tibial canal and sorrunded sof tissue.

CRP and ESR prior to the surgical event will be requested as the patient's reference value. Subsequently, ESR and CRP will be evaluated within the first 5 days after surgery and subsequently, within 4, 6, 8 and 12 weeks. If during these gatherings the CRP > 93 mgs/dl and ESR 44 mm/hr, they will undergo aspiration of joint fluid. If leukocytes are > 1200, the diagnosis of Acute Periprosthetic Infection will be obtained.

**Statitical Analysis Plan**

The results of ESR, CRP as well as the presence of risk factors and the prevalence of infection will be collected in a data sheet (appendix 2). Once all the results have been obtained, a statitical analysis will be carried out using T student and mesure of central tendency statistics. To evaluate the risk factors related to infection, will be use logistic regretion analysis.

**Health Economic analysis**

The study will also evaluate any health economic benefits of the experimiental group compared to the control group. To do so, the following information will be collected for each patient in the study: (Appendix 3)

- Time in operating room
- Lenght of hospital stay
- Clinical follow-up (sheduled)
- Infection following tratment (yes/no)
- Additional surgery (for same original condition)
- Amount of antibiotic therapy during stay.