Using a condom to prevent cement interdigitation into bone during the first stage of a two-stage revision arthroplasty for a periprosthetic joint infection

By

Dr Jannie Oosthuizen

Registrar Department of Orthopaedic Surgery

University of the Free State

Student number: 1997288053

Supervisor:

Dr Johan van der Merwe

Senior Consultant Department of Orthopaedic Surgery

University of the Free State

SUBMITTED TO THE UNIVERSITY OF THE FREE STATE

A thesis submitted in fulfilment of the requirements for the degree of MMed in Orthopaedics

Faculty of Health Sciences

School of Clinical Medicine

Department of Orthopaedics

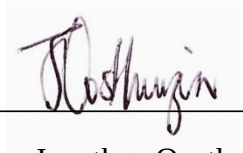
2018

Content:

PLAGIARISM DECLARATION

I, Jan Jonathan Oosthuizen, declare that this study was conducted by me and is solely my own work. It furthermore has not been submitted or presented for evaluation for any degree at any other university. I did not commit any plagiarism nor did I unlawfully copy any information from another author. I have included all sources I have used and this has been indicated and acknowledged in my references.

Signed on 13 March 2017 in Bloemfontein.



Jan Jonathan Oosthuizen

SUMMARY OF STUDY

Introduction and Aims: Total joint replacements are a universally accepted treatment in patients with end-stage osteoarthritis, post-traumatic arthritis, inflammatory arthritis, avascular necrosis of the femoral head as well as developmental dysplasia.[1,2] Due to an ageing population the demand for these procedures are increasing. On the other hand complications associated with arthroplasty will also increase. It can be argued that the most devastating complication following arthroplasty is infection. Prosthetic infections are difficult to treat and usually requires revision surgery. Whether the revision is done in a single stage or as a two-staged procedure, it remains a challenge to remove the infected prosthesis and replace it with a temporary antibiotic spacer. If the spacer is inserted as for a primary or uninfected revision replacement, interdigitation of the cement into the interstitial spaces of the bone occurs. In non-infected primary or revision surgery this is desirable as this strengthens the bone-cement-interface resulting in a stable prosthesis. Once an implant becomes infected and a two-stage revision is planned, the very same strong bone-cement interface presents a serious problem. Removal of these infected implants can be very time-consuming. If one can prevent interdigitation of the cement at the time of insertion of the temporary cement spacer, it may significantly shorten the second stage of the procedure and possibly prevent complications.

The purpose of this study is to determine if the interdigitation of bone cement into bone can be prevented by using a standard, government issued male or female condom during the first stage of a two-staged revision procedure.

Methodology: The study was conducted in the dissection hall of the Department of Anatomy of the Faculty of Health Sciences at the University of the Free State. Eleven cadavers were available at the time of conducting the study. Standard government issued male and female condoms were used. A cross-sectional study design was used and the data was analysed by the Department of Biostatistics at the University of the Free State.

Results: Twenty-one femurs and thirteen tibias were used. In the femur, we used a male condom in eleven cases and a female condom in ten cases. The condom was intact in one case and ruptured in ten cases when a male condom was used in the femur. No interdigitation of cement was seen during visual inspection in any of these cases. When a female condom was used it was intact in seven cases and not intact in three cases and no interdigitation was also noted in any of the cases.

In the tibia we used a male condom in eleven and a female condom in two cases. The male condom was intact in eight cases and it ruptured in three cases with no interdigitation of cement noted. A female condom was used in only two cases and was intact in both of these with no interdigitation of cement on visual inspection. Without exception all the condoms, male and female, ruptured at the distal end covering the tip of the prosthesis whilst the part of the condom surrounding the prosthesis proximal to tip were intact and therefore prevented interdigitation of the cement. Although interdigitation was not observed in any of the cadavers, we found a statistical significant difference between intact male and female condoms when used in the femur ($P = < 0.05$). There was no statistical difference between intact male and female condoms when used in the tibia ($P > 0.05$). There was however a statistical significant difference when the intact condoms used in the tibia were compared to the intact condoms in the femur ($P < 0.05$).

Conclusion: Our findings suggest that either a male or a female condom may be used to prevent interdigitation of cement into the trabecular bone. Using a standard government issued female condom is easier and more reliable when compared to using a standard government issued male condom. The utilization of a condom in the femur proved to be troublesome due to various reasons. Our study furthermore indicates that it is better to use a female condom in the femur. No cement interdigitation was noted upon inspection regardless of the condom used.

Recommendations: We recommend that a standard government issued female condom may be used to prevent the interdigitation of cement into the trabecular bone in both the proximal femur and proximal tibia. The use of a male condom should be reserved for use in the tibia.

Despite our findings in cadaveric models, further *in vivo* research is necessary before the technique can be advocated as safe to use in patients. Another study investigating the sterility of the condoms that were used are currently being undertaken at the UFS.

Keywords:

Revision arthroplasty, prosthetic joint infection, interdigitation of cement, condom.

1. INTRODUCTION

Total joint replacements are a universally accepted treatment in patients with end-stage osteoarthritis, post-traumatic arthritis, inflammatory arthritis and in the hip, avascular necrosis of the femoral head as well as developmental dysplasia of the hip.[1,2] The procedure provides pain relief, increase the range of movement of the affected joint, improves the quality of life and restore the functionality of patients. During the past few decades arthroplasty procedures are performed more regularly and it is estimated that 4 million total hip and/or knee replacements will be performed annually by 2030 in the United States. As the demand for these procedures continue to increase due to an continually ageing population, so will the burden of the complications associated with arthroplasty also increase.[3]

Common complications associated with replacement surgery includes loosening of the prosthesis, wear and associated osteolysis, instability, periprosthetic fractures and infection or implant sepsis.[1] It can be argued that the most devastating complication following arthroplasty is infection. Prosthetic joint infections are notoriously difficult to diagnose and subsequently treat. The overall incidence of periprosthetic joint infections are however quite low, between 1 and 2 %. There are however reports of infection rates of as low as 0.3% (British Medical Research Council) to as high as 7-16% (Scandinavian Arthroplasty Report). Treating these infections results in an increased economic burden as the cost of the surgery is increased by 76% in the case of total hip replacements and 52% in total knee replacements. One can therefore argue that in order to contain the costs involved, methods to decrease the economic burden should be explored.[3]

Modern sterile techniques, unidirectional airflow systems and the use of pre-operative prophylactic antibiotics resulted in lower infection rates in joint replacement surgery. As mentioned before, the current infection rate is approximated at 1% to 2.5% but one must take into consideration the annual number of primary arthroplasty procedures that is increasing due to an ageing global population.[2] In order to decrease patient morbidity and minimize the economic impact of infected joint arthroplasty, efforts directed at improving the management of deep periprosthetic infections should continually be explored. This paper will propose a technique that might be utilized successfully in the treatment of prosthetic joint infections.

1.1 Background / Literature review

Periprosthetic joint infections are a common problem encountered by the orthopaedic surgeon. Prosthetic infections usually requires revision surgery, leads to significant limitation and less satisfaction in the patient, long hospitalizations and very expensive procedures to treat and eradicate the infection.[4] Whether the revision is done in a single stage or as a two-staged procedure, it remains a challenge to remove the infected prosthesis and replace it with a temporary spacer, with or without antibiotics. In the hip, removing both the acetabular and femoral component is demanding, time consuming and not without risks and complications. Complications of implant removal include bleeding, femoral or acetabular fractures and perforation. Not only is it a technically difficult procedure in the most experienced of hands, it also contribute greatly to increase costs as it is generally difficult to remove these implants which leads to increased operating times and subsequently increased costs due to longer anaesthetic times. The same applies to the removal of implants after a knee replacement.

1.1.1 Mechanism of infections

According to Hernigou *et al.* four main mechanisms leading to infection of a prosthesis has been described.[5]

1.1.1.1 Intra-operative contamination:

This was previously the most common mechanism by which an infection was caused but the use of pre-operative prophylactic antibiotics have altered this mechanism. Currently intraoperative contamination contributes only to a few cases of orthopaedic implant infections.

The infection following intraoperative contamination has two clinical patterns:

- An acute postoperative infection (very rare). Diagnosis is made on the basis of clinical signs such as inflammation of the wound accompanied by fever. The infection is contained within the soft tissues with no osteitis present.

- The second clinical pattern is characterized by gradual loosening of the prosthesis over time (most common presentation). Loss of function is characteristic of this infection. Osteitis is almost always present.

1.1.1.2 Delayed contamination:

This is now a common mechanism in modern times. The prosthesis, which is sterile upon implantation, is contaminated by bacteria located elsewhere in the body. The spread of the infection is usually haematogenous but spreading of the bacteria can also be via the lymphatic system. The most typical and common presentation is one of delayed contamination after several years of satisfactory function. Pain in the hip along with fever develop in a patient who has an active focus of infection elsewhere. An infection of the skin, teeth, lungs or urinary tract is often the source. Haematogenous contamination can however also occur in the immediate postoperative period as a result of a lung, urinary tract or catheter-related infection.

1.1.1.3 Contamination by means of direct spread:

This mechanism of infection occurs mainly in the knee but it can also occur in the hip after joint replacement surgery. In the hip it occurs mainly in association with repeat surgery following a periprosthetic fracture.

1.1.1.4 Infections related to reactivation of an indolent infection:

These infections mainly occur in patients who had previous hip surgery, such as a femoral osteotomy or surgery for an acetabulum fracture, prior to joint replacement surgery. The infection is unrecognised until it is reactivated by implantation of the prosthesis.[5]

1.1.2 The concept of biofilm

A biofilm can be described a structured aggregation of microbial cells of one or several species, encased in a self-produced matrix and adherent to a biotic or abiotic surface (Crampton *et al.* 1999; Rice *et al.* 2007; O'Neill *et al.* 2008). The biofilm matrix is composed of exopolysaccharides, proteins, teichoic acids, lipids and extracellular DNA.[6,7]

Biofilms are commonly associated with a foreign body including implanted prosthetic joints. These abiotic artificial surfaces offer a surface to which bacteria can attach and eventually form a biofilm. The surfaces of commonly used orthopaedic implants, such as titanium (and its alloys), stainless steel, cobalt-chromium, various polymeric biomaterials (such as ceramics, hydroxyapatite and polyethylene), and polymethylmethacrylate (PMMA) cement are all susceptible to colonization by biofilm-forming bacteria.[6]

Biofilm bacteria can cause extreme modifications to the local environment and this usually acts in their favour.[8] A biofilm therefore create an ideal microenvironment favourable to the reproduction of bacteria rendering them resistant to antibiotics and the patient's immune system. Once a biofilm has formed, it can be extremely difficult to eradicate the infection. In the field of arthroplasty, preventing and treating biofilms is a major obstacle to effectively manage prosthetic joint infections and reduce infection rates.

1.1.3 Diagnosis and classification of periprosthetic joint infections

In order to diagnose a prosthetic infection, a high index of suspicion is needed backed up by laboratory tests.[3,9] No single clinical or laboratory test has been shown to have the ideal sensitivity, specificity and accuracy fir the diagnosis of periprosthetic joint infections.[10] In order to make the diagnosis of a periprosthetic joint infection, a stepwise approach has to be followed as recommended by Della Valle *et al.* in 2010 (Figure 1) and amended by Parvizi *et al.* in 2016. This stepwise approach starts with a good history and a thorough clinical examination followed by imaging studies and blood tests. If the diagnosis is still unclear, the joint can be aspirated in theatre and the aspirated fluid sent in for microbiological testing.[3] Recently newer diagnostic modalities looks promising to aid in the diagnosis of infections including the use of alpha-defensin or interleukin-6 levels.[20]

The Musculoskeletal Infection Society proposed a series of major and minor criteria in 2010. These criteria can be used to assign a numerical value to the serological markers. In order to consider the diagnosis of a periprosthetic joint infection, one of the major criteria must be met and three of the minor criteria should be present:[3,11]

Major criteria (one)
• Two positive periprosthetic cultures (from fluids or tissues). • The presence of sinus tract that communicates with the joint.
Minor criteria (three)
C-reactive protein (CRP) level: • > 100 mg/L in acute infections. • > 10 mg/L in chronic infections. **Erythrocyte sedimentation rate (ESR) level:** • > 30 mm/hr (only applicable in chronic infections). **Elevated synovial leukocyte count:** • > 10 000 cells / μL in acute infections. • > 3000 cells / μL in chronic infections and / or • + + or more in leukocyte esterase dipstick test. **Elevated synovial neutrophil percentage (PMN cells):** • > 90% in acute infections. • > 80% in chronic infections. **Other:** • Positive periprosthetic histological analysis (> 5 neutrophils / field). • A single positive culture (fluid or tissue).

Prosthetic joint infections can also be classified according to the time of onset of symptoms as described by Trampuz and Zimmerli (Zimmerli *et al.* 2004, Trampuz and Zimmerli 2008):[12]

a) Early infections:
- < 3 months post-operatively
- Typically caused by highly virulent microorganisms (Staphylococcus aureus, Gram-negative bacilli such as E. Coli)

b) Delayed infections:
- 3-24 months post-operatively
- Typically caused by less virulent microorganisms (coagulase negative staphylococci, priopionibacterium acnes)

c) Late infections:
- > 24 months post-operatively
- Typically caused by virulent bacteria (staphylococcus aureus, streptococci and Gram-negative bacilli)

1.1.4 Current concepts in revision surgery

Once the diagnosis of a periprosthetic joint infection has been made, the orthopaedic surgeon has to make a decision regarding further management of the infection. The goal of management is not only to eradicate the infection, but also to preserve function by protecting the bone stock as well as the muscle function.[5] The decision on the most effective treatment approach for an infected prosthesis is still a controversial topic. Despite advances in the field of revision surgery there are still questions remaining regarding the best approach.

- A common question is whether the revision procedure should be done in one or two stages?
- In the case of an acute infection, should the prosthesis be exchanged or will a soft-tissue debridement be sufficient?
- Is a resection arthroplasty superior to an exchange arthroplasty in controlling the infection?
- In the case of an exchange arthroplasty, should one use a cementless prosthesis or will an antibiotic-loaded cement spacer improve results?

1.1.5 Management of prosthetic joint infections

The management of periprosthetic joint infections consists of one or more of the following techniques:[3,5,13]

- Antimicrobial treatment
- Debridement and irrigation
- Resection arthroplasty
- Exchange arthroplasty (single stage revision or two-stage revision)
- Arthrodesis
- Amputation

1.1.5.1 Debridement, irrigation and cleaning with retention of the prosthesis:

Acute infections can be treated with debridement and irrigation. Indications for debridement and irrigation include:[3]

- An acute infection developing within 30 days after the surgery,
- No implant loosening should be present,
- An acute haematogenous infection,
- Implantation of the prosthesis within the past 3 months.

Contraindications include:

- Wound not healing by primary intention,
- The presence of a fistula,
- Evidence of prosthetic loosening.

The original incision is reopened and the prosthesis dislocated. Infected soft tissues are then excised and the extraosseous parts of the prosthesis is cleaned but not removed.

This procedure is highly recommended if an infection develops within the first 3 weeks after the initial surgery.[5]

1.1.5.2 Resection arthroplasty in chronic infections:

In this case most patients have radiological evidence of both endosteal osteolysis as well as a periosteal reaction around the femur. Both the cup and the femoral stem is affected by osteolysis. The diagnosis is confirmed by means of joint aspiration. Resection arthroplasty involves removing the infected prosthesis with or without parts of the bone, for example a girdlestone procedure. Resection arthroplasty is however associated with poor function when compared with exchange arthroplasty. It should therefore be reserved for patients in a poor medical condition who have a history of failed prosthesis-sparing surgery.[5]

1.1.5.3 Exchange arthroplasty (single stage and two stage procedures):

One of the ongoing controversies is whether to revise a chronically infected total joint replacement in one or two stages. According to literature some authors and centres advocate doing the revision in two stages whilst others use strict criteria where after they perform the surgery in one or two stages. Some authors believe that the revision should (almost) always be done in a single stage.[14]

Single stage revision surgery:

During this procedure all the infected prosthetic components, including the bone cement are removed, the infected tissues are aggressively debrided followed by re-implantation of a new prosthesis with antibiotic-loaded bone cement. Medical treatment of the infection include specific intravenous antibiotic treatment for 2 to 6 weeks followed by oral antibiotics for a period of 3 months. Rifampicin is commonly prescribed due to its activity against organisms producing a biofilm on the prosthesis.

Indications for a single stage revision include:

- Relatively healthy patient,
- Minimal bone loss,
- Viable soft tissues,
- Low virulence organism (sensitive Staphylococcus aureus, Enterococci, excluding organisms like pseudomonas and gram-negative bacteria) and
- The organism should be susceptible to oral antibiotics with excellent bio-availability.

Advantages of a single stage procedure:

- Lower costs (for patient/medical aid/hospital)
- Avoiding a second procedure and
- Lower morbidity rates.[3]

Despite the advantages of a single stage procedure, it is not commonly used in most centres due to the fear of incomplete irradiation of the infection resulting in a chronic infection. This technique reports a success rate of more than 80% for eradicating the infection if done in specialized departments where a multidisciplinary team is used.[3]

Two-stage revision surgery:

The two-stage exchange arthroplasty remains the gold standard for the treatment of periprosthetic joint infections following total hip replacement.[15] This is the technique of choice in many centres for the treatment of chronic periprosthetic infections. During the first stage of the procedure, the infected prosthetic components and bone cement are once again removed and the tissues are aggressively debrided. A cement spacer loaded with antibiotics is then placed in block or articulated (to preserve the space and avoid soft tissue contractures).

The patient is then started on intravenous antibiotics for a period of 4-6 weeks followed by no antibiotics for another 2-8 weeks (most common regimen). Rifampicin is usually not prescribed as the prosthesis is removed during the first stage (no hardware for biofilm to form on).

Indications for a two-stage procedure include:

- Chronic periprosthetic infections,
- Minimal bone loss,
- Adequate host,
- Patient willing to undergo two surgeries,
- Patients with actively draining fistula's and
- High-virulence organisms (MRSA, Candida).

This technique reports a success rate of 87% for eradicating the infection and should be tailored according to the severity of the infection.[3]

1.1.5.4 Arthrodesis

Although this is a useful form of treatment, the procedure has very few indications due to the associated morbidity. The procedure involves an arthrodesis of the limb / joint to allow ambulation and avoid amputation.

Indications for an arthrodesis include:

- Patient that are not walking,
- Significant bone loss,
- Little and poor quality soft tissues,
- High-virulence infections (with low bioavailability antibiotics),
- Poor general condition of the host and
- Failed two-stage revision surgery.

Arthrodesis can be achieved by using an intramedullary rod, an external fixator or internal plating. Eradication rates of 60 – 100% are reported in literature.[3]

1.1.5.5 Amputation:

When all other attempts to control the periprosthetic infection has failed, amputation is often the last resort to eradicate the sepsis. The procedure is reserved for a select group of patients and indications include:

- Necrotizing fasciitis not responding to debridements,
- Severe bone loss,
- Soft tissue defects that cannot be closed primarily,
- Failed resection arthroplasty or arthrodesis and
- Non-ambulatory patients.

The technique consists of an amputation or disarticulation of the affected limb.[3]

1.1.6 Use of antibiotic spacers

The use of antibiotic-loaded spacers are commonplace in the current management of prosthetic joint infections. The primary goal of using a spacer is to assist in eradicating the infection.[16] Various techniques and devices have been developed and tested in an attempt to improve the management of infected prosthesis. The specific use of these antibiotic-loaded spacers in especially two-staged revision surgery has many benefits including:

- Early joint and patient mobilization,
- Shorter hospital stays,
- Potentially a reduced rate of chronic or re-infections,
- Preservation of limb length and
- Minimizing soft-tissue contractures.

1.1.6.1 Classification of available spacers

Over the past two decades, the use of antibiotic-loaded cement spacers in prosthetic joint infections increased and became fairly popular amongst orthopaedic surgeons.[8] Spacers can be classified into non-articular or articular spacers.[18,19]

a) Non-articular spacers:

- Also known as block or static spacers as they do not allow motion at the joint.
- The use of block spacers was first reported in 1988 by Cohen *et al.* and Wilde and Ruth.
- The spacer consist of polymethylmethacrylate cement and is impregnated with antibiotics.
- These spacers are usually made in the operating room at the time of surgery and moulded to fit the bone it is intended for after removal of the infected prosthesis.
- The antibiotic-impregnated cement delivers higher local concentrations to the local environment and also preserve the articular space.

- Static spacers are commonly used in the knee characterized by severe bone loss as a mobile spacer cannot maintain stability in these cases.
- These type of spacers can be considered as a temporary knee arthrodesis.

Advantages:

- Improved eradication of the infection with better pain relief.
- Significant lower cost when compared to articulating spacers that are often pre-manufactured.
- Usually indicated in patients who has ligamentous laxity, an insufficient extensor mechanism or in patients with massive bone loss due to the infection.

Disadvantages:

- The knee must be kept in extension with as little as possible flexion.
- Cast immobilization or the use of a knee ranger is necessary after implantation.
- The spacer can dislodge and lead to bone erosion.
- The second stage of the revision is still difficult due to scar tissue formation, interdigitation of the cement into the bone, tissue adherence to the spacer and shortening of the quadriceps.
- The main drawback of static spacers are loss of movement with associated joint stiffness and poor range of movement after the second stage of the revision.[3]

b) Articular spacers:

- Also known as mobile or dynamic spacers.
- The main characteristic of these type of spacers are that they allow flexion and extension at the knee or hip joint in-between the two surgical stages.
- They also function to maintain the joint space and serves as a vehicle to deliver high concentrations of antibiotics to the local environment.
- Several techniques have been described to create a dynamic spacer by using different types of interfaces.
- The different interfaces used include cement-on-cement, prosthesis-on-polyethylene and metal-on-polyethylene constructs.

Advantages:

- Preserve range of movement.
- Local delivery of antibiotics.

Disadvantages:

- Commercially manufactured off-the-shelf dynamic spacers come in limited sizes with limited antibiotic doses.[3]

Types of articulating spacers:[18,19]

1. Temporary prosthesis from re-sterilized or new components
2. Cement spacers that are moulded at the time of surgery
3. Preformed or commercial spacers.

1. Temporary spacers:

Scott *et al.* described a technique where the original prosthesis is sterilized in the autoclave and then re-implanted into the patient using antibiotic-loaded cement. The second and final stage of the revision was performed at 6 weeks. Hoffman *et al.* described a similar technique in 1995 where used the same sterilized tibial and femoral components but a new polyethylene tibial insert. He fixated the spacer by using antibiotic-impregnated bone cement mixed in a ratio of 4.8 grams of tobramycin in 40 grams of cement. The cement was then applied to the bone at the end of the working phase to mould the surfaces without deep interdigitation.

2. Cement spacers that are moulded at the time of surgery:

McPerson *et al.* presented the technique of using a handmade mould of a total knee arthroplasty that he made from antibiotic-loaded cement to be used as a temporary spacer during two-stage revision surgery. Although it was difficult to maintain stability, the spacer allowed some knee function. Another intra-operatively moulded spacer was introduced by Duncan *et al.* he used plastic moulds to obtain smooth articular surfaces. This spacer is a replica of a total knee replacement made entirely of antibiotic-loaded cement known as the Prostalac® system.

3. Preformed or commercial spacers:

Castelli *et al.* recently introduced an articulating spacer that was preformed. These spacers are made exclusively from acrylic cement that is impregnated with the antibiotic gentamycin and is called the Spacer-K. The tibial and femoral components are both available in three different sizes. These spacers are also fixed to the bone by using antibiotic-loaded cement and allows partial weight-bearing and range of movement exercises of the knee during the two stages.

1.1.6.2 Complications of cement spacers

The use of cement spacers are not without complications. Although widely used in the management of prosthetic joint infection, they might give rise to several complications occurring in between stages and therefore compromise the functional outcome. Besides complications such as re-infection and/or persistence of infection, mechanical complications such as spacer or femoral fractures and spacer dislocation can also occur. These complications are however rare and the exact incidence is not known.[17]

1.1.7 Cost comparison

As mentioned before, various options are currently being utilized in a two-stage revision procedure for an infected joint replacement. One option is to remove the initial implants / prosthesis, sterilize it and cover it with antibiotic-loaded bone cement. This implant is then re-implanted and used as an antibiotic cement spacer (which is removed during the second stage of the revision procedure and replaced with a new implant). This is a well described procedure as noted before. Another option is to make use of a commercially made mould. The bone cement is poured into a plastic mould (femur stem or knee components). Once the cement has set, the plastic casing is cut open and the mould removed. This mould is then implanted to be used as a temporary spacer. If the initial sterilized procedure is used, the cement is moulded around the prosthesis and the implanted as a spacer – interdigitation of the cement into the trabecular bone will follow resulting in a stable bone-cement interface.

When a commercial mould is used, interdigitation will not take place as the cement is setting within the plastic covering / mould – interdigitation does therefore not take place which ensures easy removal of the spacer during the second stage of the revision surgery. Despite this obvious advantage, these moulds come at a price. A standard femur mould (Zimmer®) cost about R 8294.52 excluding the bone cement used to make the prosthesis in the mould. Two packets of cement (Palacos® with gentamycin) are usually used in this mould at a price of R 4304.72. This adds up to a total of R 12 599.24 for a standard femoral mould. A typical total knee replacement mould (tibial and femoral component - Copal®) cost about R 5 500.00, once again excluding the cement. This adds up to a total of R 9 804.72 when the cement is included.

If the initial prosthesis is used as a temporary spacer, one only need to apply the antibiotic-loaded bone cement resulting in a total amount of R 4304.72. This is a reduction of > 50% when compared to the commercial moulds. The drawback of this technique however is interdigitation of the cement. This would be an even more attractive option if cement interdigitation can be prevented. Examples of quotations obtained is attached in Appendix C.

1.1.8 Prevention of periprosthetic joint infections

The World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC) recently published new guidelines for the prevention of surgical site infections. The proposed strategies were reviewed by Parvizi *et al.* and published in the The Bone and Joint Journal in April 2017.[20]

1.1.9 Future directions in managing periprosthetic infections[3]

Despite all the efforts to prevent and manage periprosthetic infections effectively, the incidence of infections still ranges between 1 and 2 %. Most actions are focused on improving diagnostic tools and to combat the biofilm.

Diagnostic imaging studies:

The positron emission tomography (PET) scan is the imaging study that provides the most information regarding the diagnosis of a periprosthetic infection. There is however a great variability in results reported and therefore further studies are necessary to validate the PET scan as a diagnostic tool.

Biomarkers:

Currently the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most important biomarkers in diagnosing an infection. Recently interleukin-6 came under the spotlight and it has been reported that IL-6 can be an excellent biomarker to be used in the diagnosis of infection. The advantage that IL-6 offers lies in the fact that levels return to normal within a matter of days whereas CRP levels takes weeks to normalize and ESR levels months.

Samples used for evaluating biomarkers are obtained by means of a diagnostic arthrocentesis. Research shows that a CRP ELISA done on the synovial fluid is superior compared to a serologic CRP done on blood.

The best biomarker obtained from synovial fluid is however alpha-defensin. It is reported to have a sensitivity and specificity of 100% in the diagnosis of periprosthetic infections. Alpha-defensin is a peptide secreted by the cells in response to microbial byproducts. Alpha-defensin is therefore not influenced by the inflammatory process nor by antibiotics. Further research is however necessary to advocate its general use.

Prosthetic advances:

Recently prosthetic implants have been covered with silver ions. It has been reported that silver ions possess antimicrobial properties when used in a cream, gel and impregnated gauzes for the treatment of ulcers and wounds. Gordon *et al.* designed a metallic prosthesis impregnated with silver polymers which showed in vitro activity against biofilms.

Research is also being conducted where the prosthesis are covered with antibiofilm agents. Therapies directed to specifically combat the physical integrity of the biofilm shows promising results.

Intraoperative measures:

Disposable anti-bacterial coating (DAC) is used in the bone-prosthesis interface delivering a high dose of antibiotics directly to the surgical site. DAC is a hydrogel consisting of hyaluronic and polylactic acid to which specific antibiotics effective against a specific organism can be added. The gel is then applied to the surface of an uncemented prosthesis before implantation and is reported that the DAC release antibiotics locally for up to 96 hours.

1.1.10 Current practice in our unit

Surgical protocol:

The current revision protocol in our unit to treat a periprosthetic joint infection is a two-stage procedure. The prosthesis, including the bone cement, is removed during the first stage of the revision surgery, a proper aggressive debridement of the soft tissues and bone is performed and a temporary antibiotic-loaded spacer is inserted. We clean the original prosthesis by removing all cement debris from it and then send it to CSD to be sterilized. We then use antibiotic-loaded bone cement and also superficially coat the spacer with vancomycin (3g in 40g of cement) where after the same prosthesis is reinserted to serve as an antibiotic spacer until the time of the second stage of the revision. During the second stage of the revision the prosthesis / spacer is removed and a new prosthesis is implanted. Before the second stage of the revision surgery the patient is evaluation for signs of ongoing sepsis by means of a clinical examination, imaging studies (XR, MRI), blood tests (CRP, ESR, WCC) and a joint aspiration (MCS). If indication of sepsis present, we proceed with the surgery. The duration between the first and second procedure is usually 6 weeks to 3 months.

Medical protocol:

The first step is to establish if there is a prosthetic joint infection or not. After taking a history and performing a clinical examination of the patient, blood is taken and the infective markers are requested (CRP, ESR, WCC). Imaging studies include either and XR or MRI. The patient is then booked for an aspiration or biopsy in theatre and samples are sent to microbiology for MCS. Once the diagnosis of an infection is made, the patient booked for a two-stage revision if indicated.

After the first stage of the procedure the patient is started on the appropriate intravenous antibiotics (according to sensitivity) for a minimum of 6 weeks. The patient is also discussed with the consultant from infectious diseases in the case of resistant organisms or if there is any doubt regarding antimicrobial treatment. Patients are then usually discharged on oral antibiotics (if available) for another 6 weeks and scheduled for the second stage of the revision. The patient will be admitted before surgery and clinically examined whilst blood tests will be repeated to evaluate for residual infection. If there is any doubt regarding infection, an aspiration will be performed prior to implanting the final prosthesis.

1.2 Aims and objectives

1.2.1 Problem Statement

Periprosthetic joint infections are commonly managed by means of a two-stage revision procedure. During the first stage the implant and cement is removed and the tissue and bone is aggressively debrided. A cement spacer containing antibiotics is then inserted to aid in controlling the infection. During the second stage of the surgery the temporary cement spacer is removed and the new prosthesis is implanted.

Using cement to fixate a temporary spacer prosthesis is a well establish practice. This is usually done with a "sloppy "cementing technique to ensure that the cement does not interdigitate with the cancellous bone. With a "sloppy" technique the bone bed is not dried, the cement is not pressurised and it is introduced at a more viscose stage. Whilst the cement is setting the prosthesis is deliberately moved to cause separation between the bone and the cement. This is easily accomplished in the case of fixation in the metaphysical part of the bone. Introducing a stemmed prosthesis in a cylinder like structure, such as the femur- or tibia shaft, creates more pressure and prohibits this sloppy technique and interdigitating inevitably takes place. This then complicates the later removal of cement and prosthesis in a deep part of the bone not easily visualized. By placing a condom between the cement and the bone this problem could be reduced. Once the cement is set the prosthesis- cement compound can be extracted and the condom removed. The prosthesis- cement compound is then reinserted.

If the antibiotic spacer is inserted in the normal way, which is as for a primary or uninfected revision replacement, interdigitation of the cement into the interstitial spaces of the bone occurs. In non-infected primary or revision surgery this is desirable as this strengthens the bone-cement-interface resulting in a stable prosthesis. The cement-bone interface represents a complex structure of acrylic bone cement interdigitating with and filling up trabecular marrow spaces.[21] Pressurization of cement into trabecular bone results in a mechanical interlock between the cement and the bone and this provides the initial fixation for the implant.[22] According to Kruger *et al.* the importance of good interdigitation between the cement and trabecular bone has been shown in various studies dealing with cemented total joint replacement. It was shown that a reduced bone-cement interface leads to a higher rate of implant loosening.[23] To achieve an optimum cement-bone micro-interlock and enhance the mechanical bond between the bone and cement, an ideal depth of cement penetration into the bone of 3-4 mm is recommended.[24] Modern cementing techniques aim to improve the mechanical interlock between bone and cement in order to establish a durable interface. Good interdigitation is a product of adequate cement penetration and resistance to bleeding.[25] Once an implant becomes infected and a two-stage revision is planned, the very same strong bone-cement interface presents a serious problem. As mentioned before, removal of these infected implants can be very time-consuming and difficult often resulting in increased costs.

If one can prevent interdigitation of the cement at the time of insertion of the temporary cement spacer, it may significantly shorten the second stage of the procedure and possibly prevent complications. It is clear that if one can weaken the cement-bone interlock, the second stage of surgery will also be technically less demanding. Benefits will include a shorter operating time resulting in decreased costs (both for the patient, hospital and medical aid), less bone loss and a decreased risk of complications such as fractures which will eventually lead to decreased

morbidity and earlier return to normal functioning. Furthermore by using the same prosthetic implant and covering it with antibiotic-loaded cement, an exact anatomical mould of the patient's femur or tibia can be made, which will lead to a superior fit when compared to a commercial mould (that comes in limited sizes). Existing voids secondary to areas of bone loss will be filled by the cement when a custom-made spacer is used.

1.2.2 Aim of the study

To determine if using a standard, government issued male or female condom can prevent interdigitation of bone cement into bone during the first stage of a two-stage revision procedure.

1.2.3 Significance of this study

The purpose of this study is to determine if the interdigitation of bone cement into bone can be prevented by using a standard, government issued male or female condom during the first stage of a two-staged revision procedure as this will lead to shorter operating times during the second stage of the surgery and prevent possible complications associated with the removal of and infected implant. It will also provide a cheaper alternative that is as effective as industry manufactured prosthetic moulds in treating prosthetic joint infections. Since the same infected implant is removed, sterilized, coated with antibiotic-loaded cement and re-implanted, it will furthermore decrease the cost to company. As mentioned before, there is a significant difference in cost between a self-made cement spacer and a pre-fabricated mould. A custom-made mould will also incorporate the patient's anatomy at the time leading to an exact fit in the intramedullary canal. This should provide some stability (in the absence of interdigitation of cement) compared to a pre-manufactured mould with limited sizing options.

2. METHODOLOGY

2.1 Research design:

A cross-sectional study was performed.

2.2 Study population:

We used male and female cadavers provided by the Department of Anatomy in the Health Sciences Faculty of the University of the Free State.

2.3 Sample size:

We were able to obtain eleven cadavers in total for this study. Both femurs and tibias of ten of the cadavers were used whilst only one tibia and one femur of one cadaver was used. This resulted in a total of thirteen tibias and twenty-one femurs that were available for the study. The initial sample size (as noted in the protocol) were increased from five to eleven cadavers as more cadavers were available at the time of conducting the study.

2.4 Exclusion criteria:

There were no exclusions as none of the cadavers had previous femur fractures and / or ORIF's and / or other surgeries performed on the femur or the tibia. There were also no cadavers who had lower limb amputations.

2.5 Measurements

2.5.1 Location:

The study was conducted in the dissection hall of the Department of Anatomy in the Faculty of Health Sciences at the University of the Free State.

2.5.2 People involved:

- Authors of the study (Dr J. van der Merwe, Dr J.J. Oosthuizen).
- Arthroplasty sales representative to assist with mixing cement (Mr P. Heyns).
- Junior orthopaedic registrar to assist with positioning of the cadavers (Dr F. Hartzenberg).

2.5.3 Equipment used:

Femoral and tibial implants:	• Arthroplasty research and development (ARD) prosthesis. • Expired tibial and femoral implants previously sponsored to the Department of Orthopaedics.
Broaches:	• Retired instruments from the Department of Orthopaedics. • Femoral broach provided by Smith & Nephew®. • Tibial broach provided by Zimmer®.
Vice grip:	• To assist with removing implants after cementation. • Provided by the author.
Battery operated saw:	• Provided by Zimmer®. • To cut the femoral neck and tibial plateau.
Bone cement:	• Expired stock sponsored by Zimmer®. • Expired stock sponsored by Smith and Nephew®.
Gloves, aprons:	• Provided by the author.
Condoms:	• Collected by the author (free, government issued condoms).

2.5.4 Procedure:

Cadavers were positioned in the lateral decubitus position and a lateral approach was used to obtain access to the femur in all cases. The femoral neck was cut using a battery operated saw provided by a representative company. A standard femoral broach was used to gain access to the femoral canal. The cement was mixed by a medical representative familiar with the technique. Once the cement reached the desired viscosity, it was applied around the femoral stem of the implant which was then inserted into a standard male condom. The femoral implant was then inserted into the femoral canal. After two minutes the implant was removed and the condom inspected for tears and spillage of the cement.

For the tibial component the cadavers were put in the supine position. The knee was flexed at 90 degrees and an anterior midline approach was used to access the proximal tibia. After the soft tissue dissection was performed, the tibial plateau was cut to ensure an even surface. A standard Christmas tree broach was used to open the intramedullary canal of the tibia. Once again the cement was mixed by the involved medical representative and after reaching an appropriate consistency, it was applied around the tibial prosthesis. The prosthesis was inserted into a standard male condom and lowered into the prepared tibial shaft. The prosthetic mould was removed after two minutes and the condom was inspected for any tears.

2.5.5 Measurements:

The integrity of the condoms and interdigitation of cement were quantified by:

- The condoms were visually inspected for perforations after removal from the femur and tibia.
- The was no need to further evaluate the condoms by using a portable 12V air compressor to evaluate for tears as all tears were objectively obvious.
- The endosteal surfaces of the femur and tibia were visually inspected for interdigitation and extravasation of cement after removal of the prosthesis from the intramedullary canal of the femur and tibia.

2.5.6 Data collection:

All data collected were transferred to a data sheet and handed over to the Department of Biostatistics for analysis.

2.5.7 Statistical Analysis:

Statistical analysis was conducted by the Department of Biostatistics at the University of the Free State using SAS version 9.4. Results were summarized by frequencies and percentages and compared statistically using Fischer's exact test due to sparse data.

2.6 Ethical Approval and Permissions

According to the World Health Organisation (WHO) ethical approval needs to be obtained when conducting any research involving humans, human remains, cadavers, tissues, biological fluids, embryos and foetuses. Therefore the researchers of this study adhered to all the ethical considerations as described by the Declaration of Helsinki:

- Permission to perform the study were obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2017/1533).

- Permission to conduct research on cadavers were obtained from all the relevant authorities including:
  a) The Dean of the Faculty of Health Sciences, Professor G. van Zyl
  b) The Head of the School of Biomedical Sciences, Professor Viljoen
  c) The Inspector of Anatomy, Professor W. Kruger
  d) The Vice-Rector of Research of the UFS, Professor C. Witthuhn
  e) The Head of the Department of Basic Medical Sciences, Dr S. van Zyl
  f) The Head of the Department of Orthopaedics, Dr S. Matshidza.

- All cadavers were treated with the appropriate respect and dignity.
- No tissues nor body parts were removed from the Dissection Hall.
- Any bone fragments and tissues were discarded in the appropriate disposal containers.

- All bones and tissues were handled with the necessary precautionary measures, e.g. wearing protective clothing (aprons), gloves and glasses.
- All personnel involved adhered to wearing personal protective equipment.
- Service delivery were not adversely affected during the time used to conduct this study.

2.7 Implementation of findings

Although our findings indicate that a condom can successfully be used to prevent the interdigitation of cement into bone in cadaveric models, further *in vivo* research is necessary to investigate their efficacy and safety in humans.

3. RESULTS

Eleven cadavers were used in the study, six were male and five were females. Twenty-one femurs and thirteen tibias were used.

In the femur, we used a male condom in eleven cases and a female condom in ten cases. The condom was intact in one case and not intact in ten cases when a male condom was used in the femur. No interdigitation of cement was seen during visual inspection in any of the cases. When a female condom was used it was intact in seven cases and not intact in three cases and no interdigitation was also noted in any of the cases.

In the tibia we used a male condom in eleven and a female condom two cases. The male condom was intact in eight cases and not intact in three cases with no interdigitation of cement noted. A female condom was used in the tibia in only two cases and was intact in both of these with no interdigitation of cement on visual inspection. Without exception all the condoms that did rupture, male and female, ruptured at the distal end covering the tip of the prosthesis whilst the part of the condom surrounding the prosthesis proximal to tip were intact and therefore prevented interdigitation of the cement.

Although interdigitation was not observed in any of the cadavers, we found a statistical significant difference between intact male and female condoms when used in the femur ($P = < 0.05$). There was no statistical difference between intact male and female condoms when used in the tibia ($P > 0.05$). There was also a statistical significant difference when the intact condoms used in the tibia were compared to the intact condoms in the femur ($P < 0.05$).

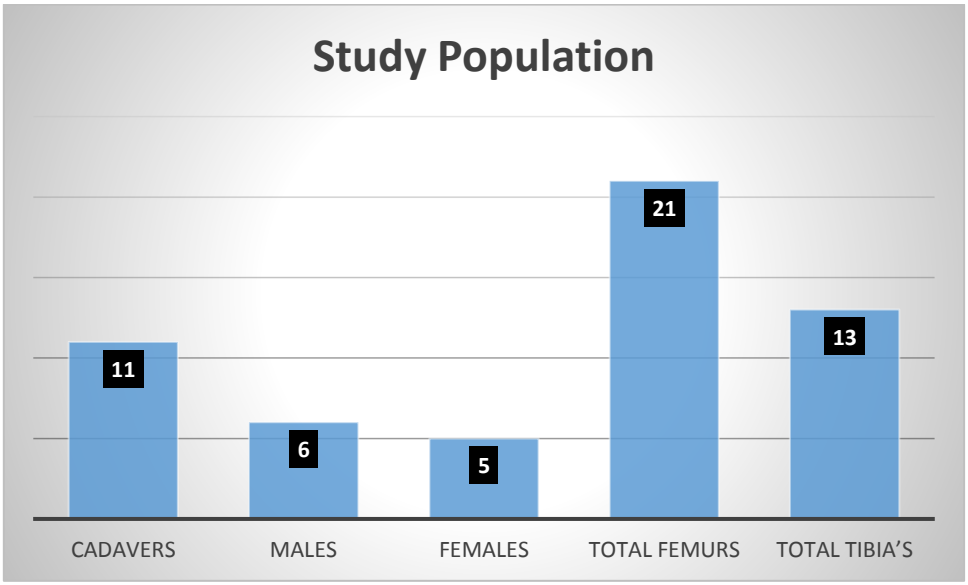


Diagram 1: Summary of the study population

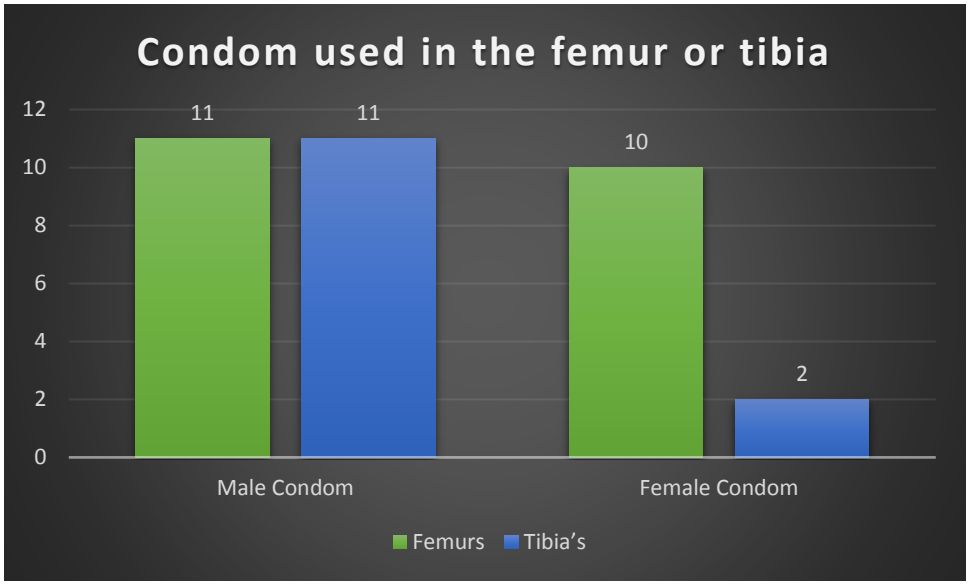


Diagram 2: Condoms used in the femur and tibia

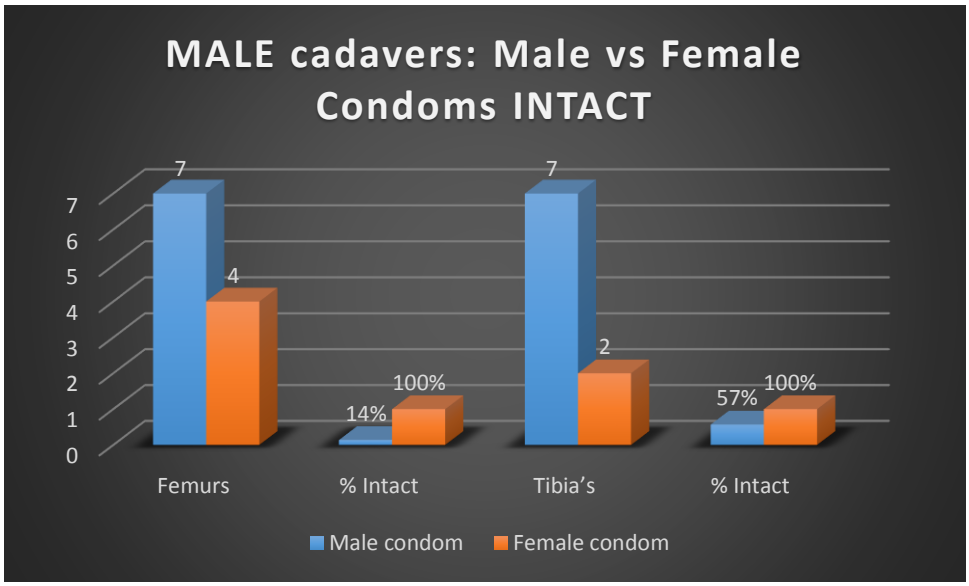


Diagram 3: Intact male and female condoms used in the femur and tibia of male cadavers

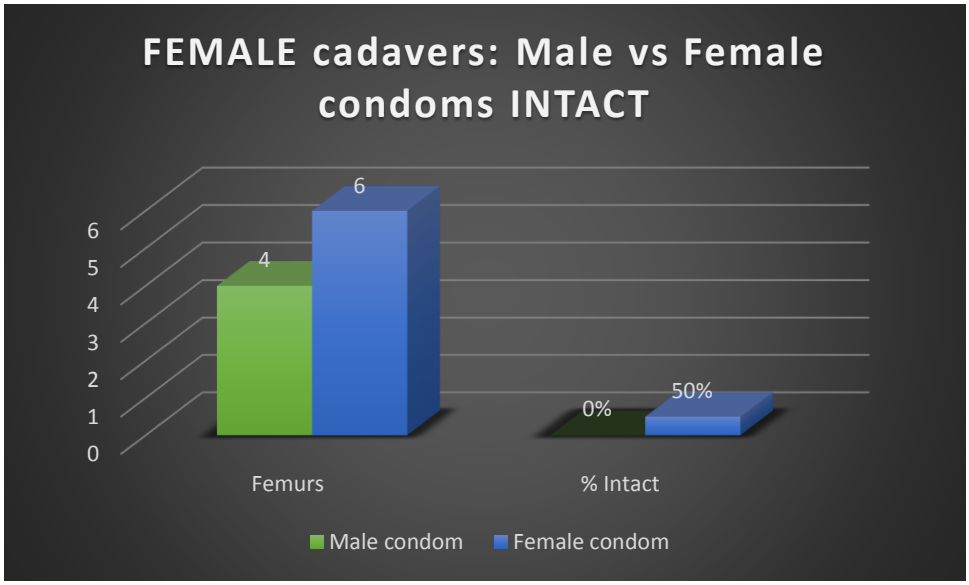


Diagram 4: Intact male and female condoms used in the femur of female cadavers

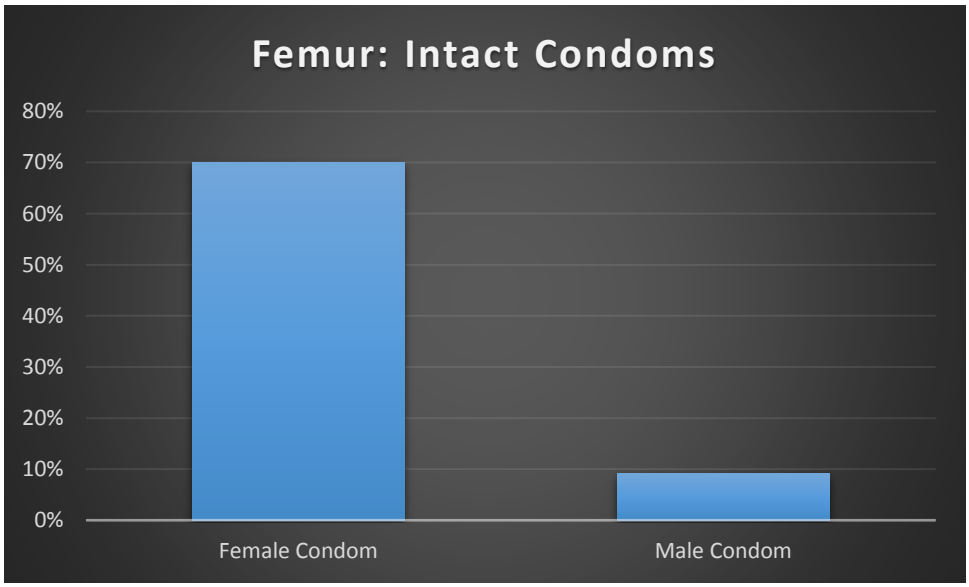


Diagram 5: Comparison between intact male and female condoms used in the femur: P = 0.0075 (P < 0.05)

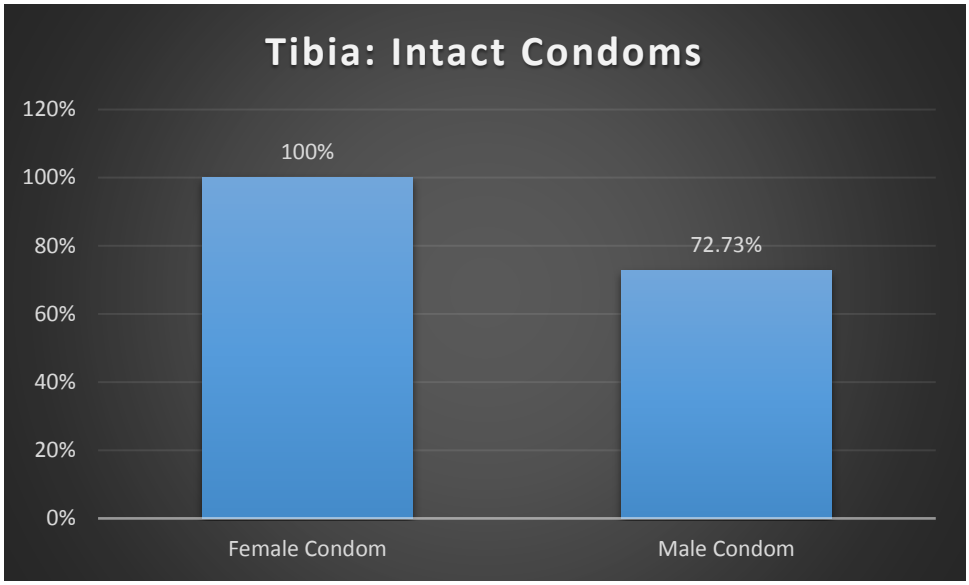


Diagram 6: Comparison between intact male and female condoms used in the tibia: P = 1.0000 (P > 0.05)

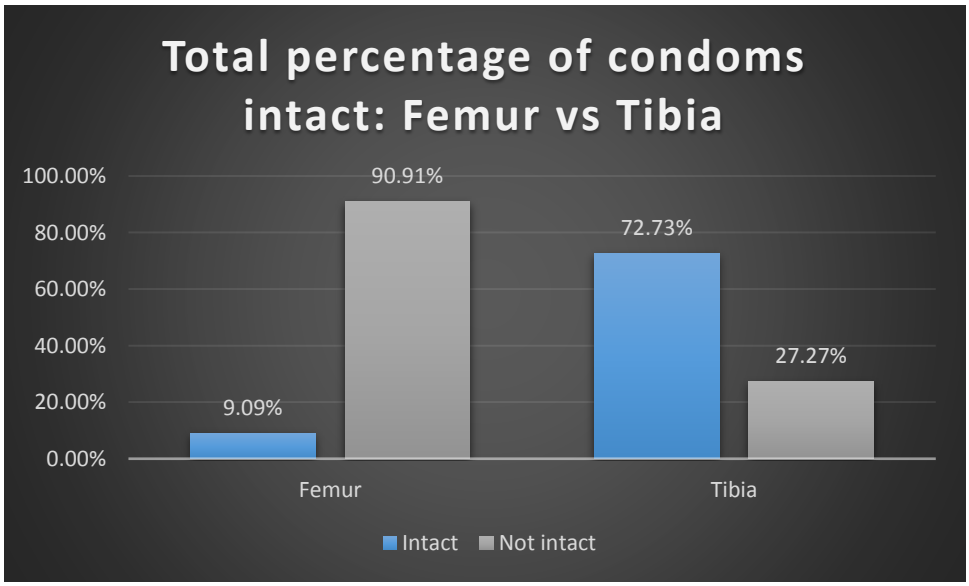


Diagram 7: Total percentage of condoms (male and female) intact in the femur and tibia: P = 0.0075 (P < 0.05)

4. DISCUSSION

We started off by applying the cement around the femoral stem of the implant and inserting the implant into a standard male condom. The implant was then inserted into the femoral canal. With the exception of one male condom, all the other male condoms ruptured upon insertion into the femoral canal. After it was evident that the male condom got caught on the rough edges of the trabecular bone inside the femoral canal, a second technique was employed where the condom was firstly inserted into the femoral canal and once in position, the femoral implant covered with cement was lowered into the canal. This technique appeared promising as there were less tension on the condom upon insertion. The condom however only remained intact in one case where a male cadaver was used. We identified a few possible causes that could lead to the condoms rupturing:

- The femurs of the cadavers we used were native in nature (no previous surgeries) and we only had one size broach available to clear the femoral shaft of trabecular bone.
- As we had to use expired femoral implants (due to the high cost of these implants) it was difficult to match the correct size implant to the size of the broach we had available. A mismatch therefore existed between the implant and the broach. In order to have a cement mantle of 2 mm around the implant to provide stability, the size of the broach and femoral implant should therefore be an accurate match.
- As the tension on the condom is increased during insertion into the femoral canal, it was stretched out and this increased the likelihood of being ruptured by the sharp edges of the trabecular bone inside the femoral canal.
- The femoral canals were fairly narrow as there was no associated bone loss as would be the case in revision surgery (where the primary implant would have been removed first with associated bone loss leading to a wider diameter and less tension on the condoms).
- Due to the anatomical variance between males and females, the femurs of the female cadavers were also smaller in diameter compared to the male cadavers.
- The normal anatomical shape of the femur, which is slightly bowed anteriorly, may also be a contributing factor that increases the likelihood of the condom being torn by the trabecular bone during insertion into femoral canal.
- The standard male condoms we used lacked strength as they were objectively fairly thin and had a narrow diameter (30 mm).

We repeated the same procedure for the next five cadavers but in this case we used a standard government issued female condom instead to assess if this will have a different outcome. The female condoms has a wider diameter (50 mm) and they are objectively thicker compared to the male condoms. We had three female and two male cadavers available. After preparing the femoral shaft in the same manner as described above, the female condom was lowered into the femoral shaft and once in position, the femoral implant covered with cement was inserted into the femoral canal (and into the female condom). The female condom remained intact in seven cases and ruptured in three cases. All the ruptures occurred in the female cadavers. This supported our finding that the size of the femoral canal had a direct influence on the tension that was put on the condom upon insertion of the implant.

Requirements for the successful use of a condom to prevent interdigitation of the cement into the trabecular bone with an infected femoral prosthesis may include:

- An adequately sized femoral canal.
- The use of a female condom.

In the tibia we also applied the cement around the stem of the tibial prosthesis and inserted the prosthesis into the condom. The male condom ruptured during insertion into the tibial canal during both attempts in the first two cadavers. Despite the condoms rupturing there was no spillage of cement into the tibial canal as the cement had already reached the dough phase before insertion. The most probable cause of the condoms rupturing is the excessive amount of tension placed on the condom as the cement-covered prosthesis was inserted into the condom before inserting it into the tibial canal. As the condom was maximally stretched it was prone to be ruptured by the trabecular bone when the prosthesis was inserted into the intramedullary canal of the tibia. As the diameter of the proximal tibia is much wider compared to the diameter of the proximal femur, this problem was easily corrected by firstly inserting the condom into the intramedullary canal and then lowering the prosthesis into the condom. This technique ensured that the condom is tension-free and eliminated the risk of being torn by the trabecular bone. We repeated this experiment in the next four cadavers (eight tibias) and we had no further rupture of the condoms. We decided to repeat the experiment with a female condom in only one cadaver as we have already proven that a male condom is sufficient to prevent interdigitation of cement into bone. The technique of inserting the condom tension-free into the intramedullary canal of the tibia and then lowering the prosthesis (surrounded by cement) into the condom, was performed successfully once again with a standard government issued female condom. It was significantly easier to produce an anatomical mould of the proximal tibial shaft as the female condom had a larger diameter with thicker walls compared to the male condom. Reasons for the successful use of a condom to prevent interdigitation of cement into the trabecular bone in the proximal tibia include:

- The wider diameter of the proximal tibia.
- The anatomical shape of the tibia which is relatively straight (not curved as is the case in the femur).

All condoms were inspected visually only and it was unnecessary to perform an inflation as it was objectively clear when the condom was ruptured. Interdigitation of the cement was prevented by the condom in all the cases regardless of the structural integrity of the condom. No cement was spilled into the femur or tibial shaft during any of the experiments.

5. CONCLUSIONS AND RECOMMENDATIONS

Our findings suggest that either a male or a female condom can successfully be used to prevent interdigitation of cement into the trabecular bone of the tibial component. The technique of using a standard government issued female condom is however easier and more reliable when compared to using a standard government issued male condom.

With regards to the proximal femur, our findings furthermore suggest that when using a standard male condom to prevent the interdigitation of cement, one will more often than not be unsuccessful. The success rate can however be improved by using a standard female condom for this purpose. Factors to consider to prevent failure include the diameter of the proximal femur and the size of the femoral prosthesis.

We can therefore conclude that using a condom to prevent the interdigitation of cement into bone is a reasonable alternative to using a premanufactured mould. Benefits of preventing the interdigitation of cement include a shorter operating time resulting in decreased costs (both for the patient, hospital and medical aid), less bone loss and a decreased risk of complications such as fractures which will eventually lead to decreased morbidity and earlier return to normal functioning. Furthermore by using the same prosthetic implant after sterilizing it and then covering it with antibiotic-loaded cement, an exact anatomical mould of the patient's femur or tibia can be made. This will lead to a superior fit when compared to a commercial mould (that comes in limited sizes). Existing voids secondary to areas of bone loss will be filled by the cement when a custom-made spacer is used.

After conducting this study we found that a standard government issued female condom can be used to prevent the interdigitation of cement into the trabecular bone in both the proximal femur and proximal tibia.

The use of a standard, government issued male condom should be reserved for use in the proximal tibia in males and females. It should only be considered in the proximal femur in patients where the diameter of the proximal femur is adequate. Milligan *et al.* investigated the relationship between the diameters of the diaphysis of the femoral canal with an increase in age. Although they concluded that the diameter of the femoral canal increases with ageing by a larger percentage in females compared to males, it was also evident that the diameter of the femur in young males was on average 1.9 mm larger when compared to the diameter in young females. In elderly males the diameter was on average 0.4 mm larger when compared to elderly females.[26]

The use of a male condom in the proximal femur may therefore be successful in elderly male or female patients, providing the female patients has a large bone structure. Patient selection therefore will be the key to obtaining a successful outcome. We therefore recommend that a female condom should rather be used in both and males and females to prevent the interdigitation of cement into bone.

Despite our findings further *in vivo* research is necessary to determine if this technique will be safe to use in patients. Another study investigating the sterility of the condoms are currently being undertaken at the UFS.

6. REFERENCES

1. Lee. K-J., Goodman, S.B. 2015. Identification of periprosthetic joint infection after total hip arthroplasty. *Journal of Orthopaedic Translation.* Volume 3: 21-25.

2. Luthringer. T.A., Fillingham. Y.A., Okroj. K., Ward. E.J., Valle. C.D. 2016. Periprosthetic Joint Infection After Hip and Knee Arthroplasty: A Review for Emergency Care Providers. *Annals of Emergency Medicine.* Volume 68(3): 324-334.

3. Vilchez-Cavazos. F., Villareal- Villareal. G., Pena-Martinez. V., Acosta-Olivo. C. 2017. Management of periprosthetic infections. *World Journal of Clinical Infectious Diseases.* Volume 7(2): 11-20.

4. Hinarejos. P., Guirro. P., Puig-Verdie. L., Torres-Claramunt. R., Leal-Blanquet. J., Sanchez-Soler. J., Monllau. J.C. 2015. Use of antibiotic-loaded cement in total knee arthroplasty. *World Journal of Orthopaedics.* Volume 6(11): 877-885.

5. Hernigou. P., Flouzat-Lachianette. C-H., Jalil. R., Batista. S.U., Guissou. I., Poignard. A. 2010. Treatment of infected hip arthroplasty. *The Open Orthopaedics Journal.* Volume 4: 126-131.

6. Gbejuade. O., Lovering. A.M, Webb. J.C. 2015. The role of microbial biofilms in prosthetic joint infections. *Acta Orthopaedica.* Volume 86(2): 147-158.

7. Patel. R., Alijanipour. P., Parvizi. J. 2016. Advancements in Diagnosing Periprosthetic Joint Infections after Total Hip and Knee Arthroplasty. *The Open Orthopaedics Journal.* Volume 10: 654-661.

8. McConoughey. S.J. *et al.* 2014. Biofilms in periprosthetic orthopaedic infections. *Future Micobiology.* Volume 9(8): 987-1007.

9. Toms. A.D., Davidson. D., Masri. B.A., Duncan. C.P. 2006. The management of peri-prosthetic infection in total joint arthroplasty. *The Journal of Bone and Joint Surgery.* Volume 88B(2): 149-155.

10. Trampuz. A., Zimmerli. W. 2005. Prosthetic joint infections: update in diagnosis and treatment. *SWISS MED WKLY.* Volume 135: 243-251.

11. Cottino. U., Rosso. F., Pastrone. A., Dettoni. F., Rossi. R., Bruzzone. M. 2015. Painful knee arthroplasty: current practice. *Curr Rev Musculoskelet Med.* Volume 8: 398-406.

12. Zimmerli. W., Trampuz. A., Ochsner. P.E. 2004. Prosthetic-Joint Infections. *The New England Journal of Medicine.* Volume 351: 645-654.

13. Gheiti. A.J., Mulhall. K.J. 2013. Periprosthetic Joint Infection: Prevention, Diagnosis and Management. *Arthroplasty update.* Chapter 22: 481-515.

14. Leite. P.S., Figueiredo. S., Sousa. R. 2016. Prosthetic Joint Infection: Report on the One versus Two-stage Exchange EBJIS survey. *Journal of Bone and Joint Infection.* Volume 1: 1-6.

15. Cooper. H.J., Della Valle. C.J. 2013. The two-stage standard in revision total hip replacement. *The Bone and Joint Journal.* Volume 95-B: Supplement A: 84-87.

16. Barreira. P., Leite. P., Neves. P., Soares. D., Sousa. P. 2015. Preventing mechanical complications of hip spacer implantation: technical tips and pearls. *Acta Orthopaedica Belgica.* Volume 81: 344-348.

17. Jung. J., Schmid. N.V., Kelm. J., Schmitt. E., Anagnostakos. K. 2009. Complications after spacer implantation in the treatment of hip joint infections. *International Journal of Medical Science.* Volume 6(5): 265-273.

18. Pitto. R.P., Spika. I.A. 2004. Antibiotic-loaded bone cement spacers in two-stage management of infected total knee arthroplasty. *International Orthopaedics.* Volume 28: 129-133.

19. Mazzucchelli. L., Rosso. F., Marmotti. A., Bonasia. D.E., Bruzonne. M., Rossi. R. 2015. The use of spacers (static and mobile) in infection knee arthroplasty. *Curr Rev Musculoskelet Med.* Volume 8: 373-382.

20. Parvizi. J., Shohat. N., Gehrke. T. 2017. Prevention of periprosthetic joint infection. *The Bone and Joint Journal.* Volume 99B(4): 3-10.

21. Verettas. D.A. 2014. Bone-Cement Interface in Total Joint Arthroplasty. In: Karachalios T. (eds) *Bone-Implant interface in Orthopaedic Surgery, pp 27-34.* Springer, London.

22. Miller, M.A., Terbush, M.J., Goodheart, J.R., Izant, T.H., Mann, K.A. 2014. Increased initial cement-bone interlock correlates with reduced total knee arthroplasty micro-motion following *in vivo* service. *J Biomech.* Volume 47(10): 2460-2466.

23. Kruger *et. al.* 2012. Cement interdigitation and bone-cement interface after augmenting fractured vertebrae: A cadaveric study. *International Journal of Spine Surgery.* Volume 6: 115-123.

24. Douglas, A., Dennis, M.D. Kowalski, R. 2015. Cement Technique in Total Knee Arthroplasty. Department of Orthopaedics, University of Colorado School of Medicine.

25. Breusch S.J., Malchau H. 2005. What Is Modern Cementing Technique? In: The Well-Cemented Total Hip Arthroplasty, p. 146-149. Springer, Berlin, Heidelberg.

26. Milligan,D.J., O'Brien, S., Bennett, D., Hill, J.C., Beverland, D.E. 2013. The effects of age and gender on the diameter of the femoral canal in patients who undergo total hip replacement. *Bone Joint J.* 2013;95-B:339–42.

Figures:

1. https://www.researchgate.net/figure/7502967_fig8_Figure-1-Schematic-cross-section-of-a-stemcementfemur-constructDashed-lines-indicate

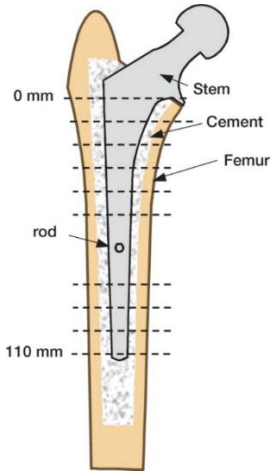
2. http://orthoinfo.aaos.org/topic.cfm?topic=a00389

3. http://eorthopod.com/artificial-joint-replacement-of-the-knee/

7. APPENDIX

7.1 Diagrammatic presentation of cemented femoral and tibial prosthesis

- Diagram 1 and 2 provides an illustration of the typical femoral and tibial prosthesis used in our study.
- Diagram 3 highlights the cement-bone-interface where interdigitation takes place.



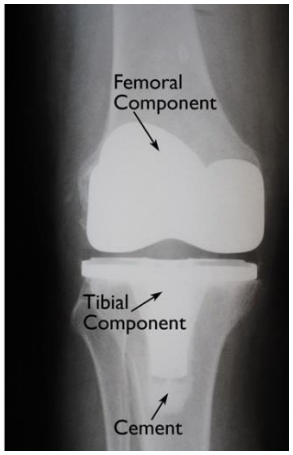
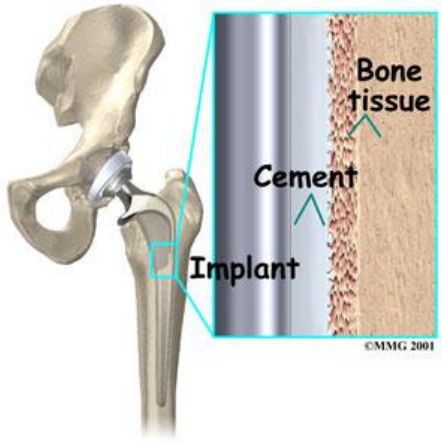


Figure 1 illustrating the femoral component of a total hip replacement[2]

Figure 2 shows the femoral and tibial component of a knee replacement[3]



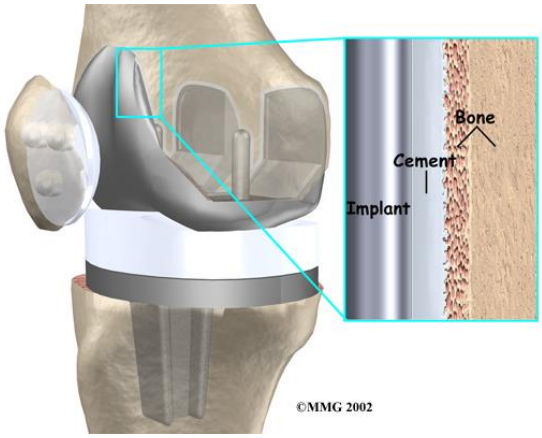


Figure 3 illustrating the bone-cement interface in the femur and tibia where interdigitation takes place[4]