RELEVANCE OF INTRA OPERATIVE BACTERIOLOGY CULTURE IN PRIMARY TOTAL KNEE REPLACEMENT

By

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LIST OF ABBREVIATIONS

TKR	Total Knee Replacement
OA	Osteoarthritis
RA	Rheumatoid Arthritis
HLA-DR4	Human Leukocyte Antigen - antigen D Related-4
PJI	Prosthetic Joint Infection
ACL	Anterior Cruciate Ligament
PCL	Posterior Cruciate Ligament
MCL	Medial Collateral Ligament
LCL	Lateral Collateral Ligament
BMI	Body Mass Index
MMP	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
PMMA	Poly-methyl methacrylate
PS	Posterior stabilizing
CR	Cruciate Retention
ESR	Erythrocyte Sedimentation Rate
CRP	C - reactive protein
PMN	Polymorphonuclear Neutrophil

HPF	High Power Field
PCR	Polymerase Chain Reaction
PET	Positron Emission Tomography
MRSA	Methicillin Resistant *Staphylococcus aureus*

ABSTRAK

Jangkitan sendi prostesis selepas pembedahan penukaran sendi adalah jarang berlaku tetapi boleh mendatangkan komplikasi yang sangat teruk. Kadar jangkitan dalam sendi selepas pembedahan penukaran sendi lutut adalah kurang dari 2%. Namun, ia tetap menjadi cabaran untuk ditangani walaupun dengan perkembangan teknik pembedahan pada masa kini. Kajian ini adalah kajian keratan rentas retrospektif. Tujuan kajian adalah untuk menentukan sama ada pengambilan swab untuk kultur bakteria semasa pembedahan penukaran sendi lutut dapat mengurangkan kadar jangkitan sendi selepas pembedahan. Sampel swab bakteria diambil sejurus selepas kapsul sendi lutut dibuka dan ia dihantar untuk proses kultur dan sensitiviti. Daripada jumlah 140 swab yang dihantar, tiada swab yang didapati positif kultur. Susulan pembedahan, didapati 2 (1.4%) pesakit mengalami jangkitan sendi dalam manakala 36 (25.7%) pesakit mengalami jangkitan sendi superfisial. Swab untuk bakteria semasa pembedahan penukaran sendi lutut mempunyai peranan yang terhad di dalam jangkaan masa hadapan terhadap insiden dan pengurusan jangkitan dalam sendi selepas pembedahan penukaran sendi lutut. Kajian ini juga menunjukkan bahawa didapati tiada perhubungan di antara faktor-faktor risiko seperti umur, jantina, obesiti, kencing manis, penyakit sendi rheumatoid, tabiat merokok dan jangkamasa pembedahan yang berlanjutan, dengan jangkitan superfisial dan jangkitan dalam selepas pembedahan.

Kata kunci: Swab bakteria; pembedahan penukaran sendi lutut; jangkitan dalam sendi; jangkitan sendi prostesis

ABSTRACT

Prosthetic joint infection following joint replacement is uncommon but can be a devastating complication. The rate of deep infection following primary total knee replacement is less than 2%. However, it remains a challenge to be encountered despite the advances in surgery nowadays. This study was a retrospective cross sectional study. The aim of this study was to determine whether obtaining bacteriology swabs for culture and sensitivity at the time of surgery could help in further reducing the rate of infection following primary total knee replacement. A bacteriology swab of the synovial fluid was taken immediately after opening the capsule of the knee joint and was sent for culture and sensitivity. Out of 140 swabs sent, none was found to be positive. Postoperatively, 2 (1.4%) of the patients developed deep infection whereas 36 (25.7%) developed superficial infection. Intra-operative bacteriology swab in primary total knee replacement has limited role in future prediction of incidence and management of post-operative prosthetic joint infection in total knee joint replacement surgery. This study also showed that there was no association found between risk factors such as age, gender, obesity, diabetes mellitus, rheumatoid arthritis, smoking and prolong duration of surgery, with post-operative superficial and deep infection.

Keywords: Bacteriology swabs; primary total knee replacement; deep infection; prosthetic joint infection

CHAPTER 1

INTRODUCTION

Knee arthritis can be defined as a joint inflammation occurs involving the knee joint which can be due to either inflammatory condition or degenerative condition. It also can be due to sequelae of infection or post-traumatic event. In particular, severe arthritis of the knee and accompanying joint symptoms result in considerable morbidity, loss of functional status, independence, and quality of life. Depending on disease aetiology, treatment options include physical therapy, analgesic and/or anti-inflammatory medications. The primary surgical treatment for severe knee arthritis is the replacement of the native knee joint with a prosthesis (total knee replacement-TKR).

Osteoarthritis (OA) of knee joint is the main clinical indication to the patient for knee replacement surgery apart from inflammatory arthritis and post-traumatic arthritis. In Western, diagnosis of osteoarthritis accounts for 94–97% of knee replacement surgery (Carr *et al.*, 2012). Also known as osteoarthrosis, it is a progressive degenerative disorder of the joints caused by gradual loss of cartilage resulting in the development of bony spurs and cysts at joint's margin. The most common joint involved is the knee joint. In Malaysia, the knee was responsible for 64.8% of all rheumatic pains pertaining to the joints, and more than half patients with knee pain had clinical evidence of osteoarthritis (Veerapen *et al.*, 2007). Apart from knee replacement surgery, other operative options are includes knee arthroscopic debridement and high tibial osteotomy. The aims of operative treatment are to relief pain, restoration of function, obtain stable joint, correction of deformity and improves the quality of life.

Advanced inflammatory arthritis especially rheumatoid arthritis (RA) of the knee joint is another common clinical indication for knee replacement surgery. Rheumatoid arthritis is a disease of unknown aetiology that affects the synovium found in joints, tendon sheaths and ligaments, resulting in deformity, weakness and loss of function. There is a hereditary component to RA, with an increased incidence of expression of major histocompatibility grouping HLA-DR4 among patients. The treatment for RA generally aimed at controlling inflammation of affected joints as rapidly as possible with medications and encourage activity to restore joint function. The knee is among the most commonly affected joints in RA which may require TKR surgery especially in advanced stage of the diseases. Despite the complexities associated with surgery in RA patients, a well-timed, well-executed TKR has been proven to enhance the quality of life for people with disabling RA of the knee (Kerner *et al.*, 2003).

Knee replacement surgery is a reliable and reproducible procedure for treating advance knee arthritis. However, there are incidence of failures and complications following surgery that have been reported. The reasons for failure in order of prevalence include polyethylene wear, aseptic loosening, instability, infection, arthrofibrosis, mal-alignment or mal-position, deficient extensor mechanism, avascular necrosis of patella, peri-prosthetic fracture and isolated patellar resurfacing (Sharkey *et al.*, 2002).

Arthroplasty-associated deep infection is a rare but can be a devastating complication. Many strategies has been suggested to reduce the risk of post-operative infection including the use of prophylactic antibiotics, decolonization of *Staphylococcus aureus*, surgical site preparations, ultra-clean air system and whole-body exhaust-ventilated suits (Bosco *et al.*, 2010). In spite of all the precautions, small group of patients have developed deep infection. The incidence of prosthetic joint infection following primary total knee replacement ranges from 0.46% to 1.55% with greatest risk within first 2 years after surgery (Kurtz *et al.*, 2010). Another study by (Peersman *et al.*, 2001) reported early deep infection rate for patients undergoing a primary knee replacement was 0.39%.

There are many confounding factors that may contribute to prosthetic joint infection. (Davis *et al.*, 1999) in their study demonstrated that a total of 63% operations showed contamination in the field of primary arthroplasty surgeries. The sites of contamination in the operating theatre are detected from gloves, gown, sucker tip, blade, needle, syringe as well as light handle. Nevertheless, the skin of the patient and airborne particles from the theatre personnel are the main source of infection (Bosco *et al.*, 2010).

The Arthroplasty Unit at Hospital Universiti Sains Malaysia, has a routine of taking intra-operative bacteriology swabs of synovial fluid in primary Total Knee Replacement (TKR). The operation theatres are equipped with positive pressure airflow system. Our believe is that intra-operative bacteriology swabs may have a role in identifying potential candidates at risk of developing an infection and may help in further reducing the rate of deep infection. Our aim in this study is to determine positive intra-operative bacteriology swabs results and its correlation with the prosthetic joint infection post primary TKR.

CHAPTER 2

LITERATURE REVIEW

2.1 Surgical anatomy of the knee joint

The knee joint is a synovial joint, modified hinge type. It is a complex tripartite joint with three distinct compartment which are; patella-femoral compartment as well as medial and lateral tibio-femoral compartments. There are four major ligaments namely anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament and lateral collateral ligament acting as a four bar linkage system in controlling the motion. Knee flexion/ extension involves a combination of rolling and sliding movement. The femur moving bodily posteriorly on the tibia as the knee flexes, so-called femoral 'roll-back'. The movement of the patello-femoral joint described as gliding and sliding. The patella moves distally on the femur with flexion, governed by its attachment to the quadriceps tendon and patella ligament. The patella acts as a pulley in transmitting the force by the quadriceps muscles to the femur and the patellar ligament.

The Anterior Cruciate Ligament (ACL) function is to resist anterior displacement of the tibia on the femur when the knee is flexed and control the screw home mechanism of the tibial in terminal extension of the knee. The ACL also resists varus, valgus and internal rotation forces of the tibia. The Posterior Cruciate Ligament (PCL) is meant to resist posterior translation of the tibia relative to the femur and allow femoral rollback in flexion range. The medial collateral ligament (MCL) restrain valgus movement of the knee joint and control of external rotation. In contrast, the lateral collateral ligament (LCL) restraint against varus rotation as well as resisting internal rotation. The medial and lateral meniscus overlay the tibial articulating surfaces. They act as shock absorber reducing contact stresses on the articular cartilage.

Mechanical axis of lower limb is an imaginary line through which the weight of the body passes. It runs from the centre of the hip to the centre of the ankle through the middle of the knee. This is altered in the presence of deformity and must be reconstituted at surgery. This allows normalization of gait and protects the prosthesis from eccentric loading. Stability of the knee joint is contributed by bony contours which give little anterior-posterior stability. Cruciate ligaments indispensable to anterior-posterior stability. Collateral ligament contribute to medial and lateral stability. Vastus muscles and their expansion retinacular contribute to stability of patella. (Moore and Dalley, 2014).

2.2 Arthritis of The Knee Joint

Arthritis or inflammation of the joint generally can be classified into several groups including non-inflammatory arthritides, inflammatory arthritides, infective arthritides and haemorrhagic arthritides. Examples of non-inflammatory arthritides are OA, neuropathic arthropathy, ochronosis and secondary pulmonary hyperthrophic osteoarthropathy. RA, juvenile chronic arthritis, systemic lupus arthritis, spondyloarthropathies and crystal arthropathies are among examples for inflammatory arthritides. The infective arthritides are best explained according to pathogenic cause which are either pyogenic, tuberculosis, fungal or spirochetes. Meanwhile, the haemorrhagic arthritides, for examples are haemophilic arthropathy, sickcle cell arthropathy and pigmented villonodular synovitis contribute in small percentage of these diseases. Among of all, primary OA, secondary OA either post-traumatic or septic joint sequelae, RA and gouty arthritis are commonly found in clinical setting affecting the knee joint that literally may lead to knee replacement surgery. Occasionally, patients with systemic lupus arthropathy, juvenile chronic arthritis, ankylosing spondylitis as well as haemophilic arthropathy may presented with knee symptoms and disability.

OA is the most common type of arthritis affected the knee joint. Risk of knee OA is contributed by a complex relations of constitutional and mechanical factors. A consistent finding in epidemiologic studies of knee OA is that the incidence and prevalence of this diseases increase directly with age. After 50 of age, women have higher rates of incident knee OA compared with men and a higher prevalence of radiographic and symptomatic OA (Felson *et al.*, 2000). Apart from age, obesity is also a strong risk factor for knee OA, particularly in women. If obesity could be eliminated, a reduction in the incidence of symptomatic knee OA could be expected in the range of 26% to 52% for men and 28% to 53% for women (Felson and Zhang, 1998). Other factors of developing knee OA include bone density, bone morphology, meniscal derangement, gender, sex hormones, and trauma.

Pathologically, OA is characterized by fibrillation and loss of articular cartilage, hypertrophic changes in the neighbouring bone including subchondral thickening and osteophytes formation, some degree of synovial change with patchy area of synovitis and areas of hypertrophy, and thickening of the joint capsule (Buckwalter and Mankin, 1997). The chondrocytes seem to be responsible for the production of most proteins at increased levels or rates in arthritic cartilage. However it also involves in breakdown of their own matrix degradation in the cartilage. Elevation of the metalloproteinases (MMP) including MMP-1, 2, 8, 9 and 13 are marked. Inappropriate activity by aggrecanase enzyme is responsible for the initial breakdown of proteoglycan aggrecan in the cartilage (Tortorella and Malfait, 2008). Although chondrocytes appear to make an attempt to repair their matrix, there is a net loss of matrix in OA.

OA is characterized by progressively increasing pain, (morning) stiffness, joint deformation, crepitation and limited range of motion of the involved joint. The Community Oriented Programme for Control of Rheumatic Disease (COPCORD) questionnaire study showed that 9.3% of adult Malaysian having knee pain with increase in pain rate to 23% in patients over 55 years old and 39% in patients over 65 years old (Veerapen *et al.*, 2007).

OA is a clinical diagnosis. The majority of people with radiologic evidence even have no symptoms of OA. On plain x-rays, it is characterized by joint space narrowing, osteophytes, subchondral cysts and subchondral sclerosis. Knee pain without radiograph changes could be interpreted as a possible sign of early OA. Symptomatic patients who with negative radiographs should be offered possibilities to study early phases of developing OA by using sensitive techniques such as magnetic resonance imaging, bone scintigraphy and biochemical markers of cartilage and bone turnover (Van Spil *et al.*, 2010). Non-operative treatment involves in combination of exercise, lifestyle modification, supplementation and analgesics. Severe OA of knee joint mandates for knee replacement surgery. As total rates of TKR have increased over time, analysis by indication uncovers a discrepancy. As expected, rates of TKR for osteoarthritis also increased substantially. In Western, diagnosis of osteoarthritis accounts for 94–97% of knee replacement surgery (Carr *et al.*, 2012).

Rheumatoid arthritis is the most common cause of chronic inflammatory joint disease. The most typical features are a symmetrical polyarthritis and tenosynovitis as well as morning stiffness. The age of onset usually is between 40 and 70 years, with women 3 or 4 times more often than men. The diagnosis of RA requires the presence of 4 of the 7 criteria according to American College of Rheumatology Diagnostic Criteria for RA. These criteria basically includes presence of morning stiffness, arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor and radiographic changes of joint erosions. There is no cure for RA. However, advances in therapy have revolutionized the treatment approach with associated major improvements in outcome (Kennedy *et al.*, 2005). The key elements in medical treatment are to identify patients with RA as early as possible, to start disease-modifying anti-rheumatic drugs with combination therapy if indicated and also to consider rapid progression to biological therapies i.e. infliximab if earlier treatment failed.

The knee joint is among the most commonly affected joints. In early joint involvement, soft-tissue procedures such as synovectomy, tendon repair and joint stabilization are more appropriate. In late rheumatoid disease, severe knee joint destruction, fixed deformity, and loss of function are among indications for replacement surgery. The surgical option of TKR is a proven technique for the management of deformity and unremitting pain in the rheumatoid arthritic knee. A multidisciplinary approach towards the management of RA, including the rheumatologist, orthopedic surgeon, and physical therapist, will ensure that the benefits of TKR are maximized (Kerner *et al.*, 2003).

Apart from OA and RA, patients with other form of knee arthritis also being treated with knee replacement surgery. Severe knee pain from chondrocalcinosis and pseudogout in an elderly patient is an occasional indication for TKR in the absence of complete cartilage space loss. Calcium pyrophosphate dihydrate crystal deposition is known to occur in metabolic disorders i.e. hyperparathyroidism and haemochromatosis. This leads to development of crystal-induced synovitis, appearance of calcific material in articular cartilage and chronic pyrophosphate arthropathy which is a type of degenerative joint disease. The crystals appears to influence the development of generalized osteoarthritis. Therefore when the progressive joint degeneration takes place, the treatment is essentially replacement surgery.

2.3 TKR as Treatment for Severe Knee Arthritis

Total knee replacement surgery was introduced and developed since 1970s and 1980s. Proper patient selection for TKR is crucial. Patients with knee OA who are not obtaining adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment should be considered for joint replacement surgery (Zhang *et al.*, 2008). The aims are to alleviate pain caused by severe arthritis and improvement of function (Rankin *et al.*, 2004). Besides, the surgery could also correct significant deformity of the joint and obtain a stable mobile knee joint. TKR is a resurfacing procedure where damaged cartilage and the underlying bone are replaced by artificial implants. It is generally accepted that presence of full thickness cartilage damage in at least one of the three compartments (medial, lateral and patello-femoral) should cause severe subjective discomfort to the patient. These could match with objective cartilage damage observed on weight bearing radiographs or other imaging techniques i.e. arthroscopy or Magnetic Resonance Imaging (MRI).

Basically there are two types of fixation in TKR surgery which are cemented fixation and press-fit fixation. Cemented fixation with poly-methyl methacrylate (PMMA) has been used as an excellent anchoring system for arthroplasty components. However, cement is prone to fatigue failure because it is a poor transmitter of tensile and shear stresses. It is also a potential source of third body wear and may increase the susceptibility to local infection. Press-fit or cementless fixation offered comparable outcome in term of implant survivorship. An analysis study reported that 15-year survival rate for cemented knees was 80.7% and for cementless knee was 75.3%. There was no significant difference between the two groups (Baker *et al.*, 2007). Press-fit fixation however is considered as technically more challenging, since a tight interface gap smaller than 0.5mm is necessary for successful component integration and immediate initial component stability.

TKR prosthesis has developed diversely. Unconstrained implant designs for TKR includes Cruciate-Retaining (CR) and Posterior-Stabilizing (PS) designs. Cruciate-Retaining is minimally constrained prosthesis that depends on intact PCL to provide stability in flexion. It could avoid tibial post-cam impingement. However in a tight PCL, there is risk of accelerated polyethylene wear. The Posterior-Stabilizing design is slightly more constraint prosthesis which requires sacrifice of PCL. Femoral component contains a cam that engages on tibial polyethylene post during flexion. Hence, it is at risk of cam jump or impingement. Another minimally constrained prosthesis which polyethylene can rotate on tibial baseplate is mobile bearing design.

Generally in patient with ligament attenuation/ laxity or exaggerated bony gap/ loss, constraint design is an option. It consists of non-hinged and hinged designs. The constraint non-hinged prosthesis is designed without axle connecting tibial and femoral component. It has a large tibial post and deep femoral box to provide varus/ valgus and rotational stability. Constraint hinged design is the most constrained prosthesis with linked femoral and tibial components. However, the well-known disadvantage of constraint design is early aseptic loosening as a result of increased constraint. Furthermore, (JÄMSEN *et al.*, 2009) has reported that there was an increased rate of infections in association with constrained and hinged prostheses in comparison with non-constrained total knee prostheses in primary arthroplasties.

In rheumatoid arthritis, the disease itself is a risk factors found to be associated with risk of developing prosthetic joint infection post TKR (Kunutsor *et al.*, 2016). The rates of infection were significantly greater in patients with RA than in those with OA, but after one year, the number of septic failures in patients with rheumatoid arthritis did not differ significantly from that in patients with primary osteoarthritis (JÄMSEN *et al.*, 2009). Careful preoperative assessment with evaluation of upper limb joints, cervical spine atlanto-axial instability, and good arc of hip movement and modulation of anti-rheumatic medications will lead to a successful outcome of replacement surgery.

2.4 Surgical principles of TKR

Proper patient and prosthesis selection are important for optimal results in TKR. Peri-operatively, prophylactic antibiotics should be administered to inhibit or eliminate contaminating microorganisms during the procedure, which reduces the probability of an infection. The first or second generation cephalosporin should be used because of its broad spectrum of action, cost-effectiveness, and the need to preserve newer and more expensive therapies. These antibiotics cover gram-positive organisms and clinically important aerobic gram-negative bacilli and anaerobic gram positive organism (Bratzler *et al.*, 2005).

Successful TKR can be achieved when proper lower limb alignment as well as soft tissue equilibrium are restored. Operative keys are inclusive of satisfactory exposure, soft tissue balance, proper alignment, and reconstruction of the patello-femoral joint. Residual medio-lateral soft tissue imbalance may lead to instability or ligament tightness. Most importantly, restoration of correct mechanical axes of the lower limb must be achieved. Pre-existing deformities should therefore be corrected during the procedure by appropriate bone resection and/ or augmentation. This osseous reconstruction should be performed in such way that mechanical joint alignment is restored while maintaining or restoring a correct soft tissue envelope around the knee joint.

Two types of surgical techniques are commonly employed to achieve this. In the 'bone referencing' technique, bony landmarks are used for restoration of osseous alignment, with subsequent soft tissues balancing after the bone cuts are made. In the 'ligament referencing' technique, the tibial cut is made first with subsequent ligament balancing. Confirmation of ligament balance by assessing the flexion/ extension and varus/ valgus balance are very crucial. The other bone cuts are performed when adequate soft tissue equilibrium has been obtained.

Mechanical alignment of the femoral and tibial component in the frontal plane should generally lie between neutral +/- 3 degree. For sagittal alignment, the down-slope of tibial component should between 0 degree and 10 degree. On the other side, the femoral component is positioned 5 to 7 degree of valgus following normal femoral anatomical axis and 3 degree rotational position which parallel to the epicondyles and perpendicular to the antero-posterior line of Whiteside. After the implantation of prosthesis, closure of knee wound ideally should be water tight in order to create an effective barrier from microbial penetration and prevent wound dehiscence. There are invention of methods of closure such as barbed sutures and adhesives to achieve this. An in-vitro study reported that liquid tight microbial barrier properties of octylcyanoacrylate tissue adhesive were effective against gram-positive and gram-negative species as well as motile and non-motile species (Bhende *et al.*, 2002). Despite that, in clinical setting, there was no statistically significant differences in infection, dehiscence, cosmesis, and general health when comparison made between adhesive, staples and sutures in wound closure for total knee arthroplasty (Eggers *et al.*, 2011). In some centres, the surgeons are preferred to put on intra-capsular drainage post-operatively to prevent haematoma formation and swelling. A systematic analysis study however reported there were no statistically significance between intervention (no drain) group and control (drain) group in term of ROM knee flexion, knee swelling, post-operative haemoglobin drop and length of hospital stay (Quinn *et al.*, 2015).

2.5 Outcome after TKR

According to studies using patient oriented evaluation and scoring systems, patients who underwent TKR have satisfactory function and relief of pain, despite substantial advances in primary TKR. Between 2 to 17 years post operatively, patients' satisfaction varied from 72–86% and from 70–84% for pain relief and functional specific activities of daily living respectively (Bourne *et al.*, 2010). There are also studies and registries to evaluate the outcome by assessing incidence of revision surgery as end-point. It is claimed to be more reliable. It was reported that 10 year risk of revision after primary TKR in patients with osteoarthritis was 4% (sundberg and Lidgren, 2015). However knee replacement in young patients remain problematic. TKR has been shown to be cost effective mode of treatment with provides significant improvements in quality of life. Resumption of physical activities after TKR lead to an overall improvement of cardiovascular fitness and general health (Aglietti *et al.*, 2005).

Although the incidence of failure after TKR is low, yet it has been reported that 22,000 knee replacements are revised every year in United States (Sharkey *et al.*, 2002). The reasons for failure are such as polyethylene wear, aseptic loosening, instability, infection, arthrofibrosis, mal-alignment or mal-positioning, extensor mechanism deficiency, avascular necrosis of the patella, and peri-prosthetic fracture. About half of the revision operations are performed less than two years after the primary operation. Previously, aseptic loosening dominated indication of revision surgery. However prosthetic joint infection and aseptic loosening are now equally often the reason for revision of TKAs (sundberg and Lidgren, 2015) because of aggressiveness in the current management of infection. The current overall incidence of infection is 0.46% to 1.55% but is higher in patients with rheumatoid arthritis, diabetes, obesity, or concurrent infection at other sites (Kurtz *et al.*, 2010).

Durability of the implant also is a great concern especially in younger patients because of the higher activity level. After 3 and half years or more, patients with osteoarthritis younger than 55 years old have almost 5 times the risk of revision compare to patients who aged 75 years or older (sundberg and Lidgren, 2015). Both long term survival as well as immediate functional performance which are obtained after TKR, therefore has a margin for further improvement and is the basis for continued research and development of knee development of knee arthroplasty design and surgical technique.

2.6 Infections after Primary TKR

Even though infection after primary TKR is uncommon, it could be a serious complication. The aetiology is multifactorial. Contamination during surgery is an important factor. Most primary knee arthroplasties are contaminated with bacteria. The contaminating skin commensals such as *Coagulase-negative Staphylococcus aureus* and *Streptococcus viridans* are transferred mostly by the operation theatre staff to various sites in the operative field. The rate of contamination is 17.8% from skin swab, 3.0% from skin blades, 1.3% from inside blade, 4.6% from suction tip and 4.4% from suture line (Byrne *et al.*, 2007). The contamination is also comes from glove tip, syringes, and gown and light handles. These could be potential risks for post-operative infection (Davis *et al.*, 1999).

There are many strategies on reducing the incidence of post-operative infection. These include the use of prophylactic antibiotics, decolonization of *Staphylococcus aureus,* surgical site preparations, ultra-clean air system and whole-body exhaust-ventilated suits (Bosco *et al.*, 2010). By developing of these strategies, the rate of contamination reduces substantially. Interestingly, positive intra-operative bacteriology swabs from primary joint replacements did not predict the occurrence of prosthetic joint infection during 5 years follow-up (Jonsson *et al.*, 2014). In this study, however, the author was unable to conclude the relationship between intraoperative contamination and PJI due to lack of control group, poor guidelines of sampling and inability to analyse as very low incidence of infection.

Apart from contamination, it is also important to identify the factors which are at increased risk of developing PJI among patients who undergo primary TKR. Both of patient risk factors and surgical risk factors ideally should be modulated in order to reduce the incidence of post-operative infections. Active tobacco use, comorbid pulmonary disease, and *Staphylococcus aureus* colonization are among significant risk factors for infection after primary TKA (Crowe *et al.*, 2015). Furthermore, a meta-analysis had reported that patient risk factors such as male gender, obesity of Body Mass Index (BMI) > $30kg/m^2$, smoker, history of steroid administration, depression, rheumatoid arthritis and diabetes mellitus are at increased risk of prosthetic joint infection (Kunutsor *et al.*, 2016). Surgical and post-operative risk factors such as prolonged operative time, simultaneous bilateral surgery, transfusion of allogenic blood units and urinary tract infection are among predictors for prosthetic joint infection (Pulido *et al.*, 2008).

Prosthetic joint infection (PJI) share similarities to acute haematogenous osteomyelitis, chronic osteomyelitis, and septic arthritis. The most common clinical symptoms is pain, apart from fever, chills, redness, drainage and sinus tracts. PJI is definite when there is a sinus tract communicating with the prosthesis; or a pathogen is isolated by culture from at least two separate tissues/ fluid samples obtained from the affected prosthetic joint. The Musculoskeletal Infection Society (MSIS) has proposed that diagnosis of PJI is met with the presence of four out of six criterion: elevated serum Erythrocyte Sedimentation Rate (ESR) and serum C- Reactive Protein (CRP) level, elevated synovial White Blood Cell (WBC) count, elevated synovial Polymorphonuclear Neutrophil percentage (PMN%), presence of purulence in the affected joint, isolation of a microorganism in one culture of peri-prosthetic tissue or fluid, or greater than five neutrophils per high-power field (HPF) in five high-power fields observed from histologic analysis of peri-prosthetic tissue at 9400 magnification (Parvizi *et al.*, 2011). PJI may be present if fewer than four of these criterion are met. There are four types of infection relevant to PJI. Acute infection is defined as infection which occurs within the first three weeks post replacement (Tsukayama *et al.*, 2003). Infection is usually confined to joint space and has not invaded prosthetic-bone interface. Late chronic infection is an infection which present for more than three weeks post operation. The organism usually creates a layer of biofilm (glycocalyx), which adhere on the surface of prosthesis within four weeks and therefore protect the bacteria from host immune system. Eradication is difficult and not uncommonly prosthesis explant is indicated in severe chronic infection. The haematogenous infection on the other hand is usually secondary to another infection i.e. dental work or infected gallbladder and may occur within days of inciting event (Tsukayama *et al.*, 2003). Type 4 infection is described as positive intraoperative cultures, which is clinically unapparent infection with 2 or more positive intraoperative cultures. The treatment protocol for patients who had positive intraoperative cultures was by intravenous administration of antibiotics for six weeks without additional operative intervention (Segawa *et al.*, 1999), (Tsukayama *et al.*, 2003).

The pathogens are usually normal skin floras, which are most common organisms include *Staphylococcus aureus*, *Staphylococcus epidermidis,* and *Coagulase-negative Staphylococcus aureus*. Candida species are the most common fungal pathogen. The standard laboratory studies used to diagnose infection include ESR, CRP, and a complete blood count with differential. CRP takes about 21 days post-surgery to return to normal while ESR takes about ninety days. If they remain elevated, it is concerning for infection. Interleukin-6 level is less commonly practiced, but it can be used to monitor progress of infection. Serum level of Interleukin-6 has the highest diagnostic accuracy with prosthetic joint infection (Berbari *et al.*, 2010).

Nevertheless, serology tests are not specific for microorganisms. Additional invasive tests are needed to characterize the infection included aspiration of the joint fluid and surgically obtained tissue samples. The joint aspiration is indicated whenever strong suspicion of infection. The synovial fluid is examined for Gram stain, cell count and culture results. Synovial WBC >1,100 cells/ml or PMN > 64% is suggestive of infection. Surgically obtained tissues are typically examined for Gram stain, culture results, and for the number of PMN white blood cells visualized per 60x HPF on frozen section. The synovial tissue biopsy has sensitivity of 100% and specificity of 98.1% compared to joint aspiration which has sensitivity of 72.5% and specificity of 92.5% (Fink *et al.*, 2008). In general, more than 5 PMN/ 60x HPF is suggestive of an infection.

One of the best techniques in diagnosis and characterization of bacterial infection is the polymerase chain reaction (PCR). This assay permits the detection of as little as one molecule of Deoxyribonucleic Acid (DNA) by generating multiple copies of the DNA target with a heat stable DNA polymerase and two oligonucleotides (16S DNA primers) that flank the DNA. If a mixture of 16S DNA primers from different genus of bacteria is used, the precise genus and species of bacteria can be identified because only a given bacterial genus' primers will amplify the DNA in question. PCR is now a standard diagnostic procedure in all microbiology laboratories. However, the definitive diagnostic test for prosthetic joint infection remains culture of tissue obtained at the time of surgery correlated with clinical findings. In other words, a positive culture must be supported by clinical signs, symptoms, and laboratory and radiographic findings.

Plain radiograph findings often show aggressive nonfocal osteolysis, periosteal bone formation, or focal lysis adjacent to an infected prosthesis. These findings are non-specific because aseptic loosening secondary to wear debris also produces similar findings. MRI investigation is difficult to be interpreted because the prosthesis may obscure the image. Therefore, bone scan which is combined with leucocyte scintigraphy is more relevant. The commonly used leucocyte scintigraphies are indium (In) 111 or technetium (Tc) 99m, as well as leucocyte scintigraphy. Another imaging method that can be considered is Positron Emission Tomography (PET) scan. It identifies high metabolic activity using fluorinated glucose.

2.7 Treatment of Prosthetic Joint Infection

Following a confirmed diagnosis, treatment of an infected TKR follows the same basic principles for treatment of osteomyelitis. The infected site must be surgically debrided to remove all of the infected necrotic tissue. Once the surgical debridement is completed, the tissues sent for culture and broad-spectrum parenteral antibiotics therapy is initiated until final culture results are determined. Specific antibiotics are typically continued for six weeks. In case of implant removal, repeat tissue sampling before re-implantation of new prosthesis has been advocated. Failure to rigorously adhere to these principles will likely result in a persistent infection. Therefore, role of non-operative treatment with suppressive antibiotic therapy is limited.

Polyethylene exchange with component retention of the prosthesis can be considered in two special circumstances: in acute infection when the diagnosis of infection is made less than four weeks of the implantation, or in early haematogenous infection when diagnosed within four weeks of inciting event (Chiu and Chen, 2007). Thorough tissue debridement and irrigation with large volume of irrigant must be performed during surgery. The modular parts should be removed to remove biofilm layer between plastic and metal parts which can act as a nidus of persistent infection. The overall success rate of this DAIR (debridement, antibiotics, irrigation, retention) technique is approximately 65% with a range from 31%-90% (Becker *et al.*, 2016). If any documented of reinfection, all implants are suggested to be removed.

In some centres, one-stage replacement arthroplasty is preferred as treatment option for prosthetic joint infection. The selection of cases depends on patient factors such healthy patient and soft tissue, no sinus tract or bone graft used, as well as pathogen factor which is low-virulence organism with good antibiotic sensitivity treated with prolonged duration of antibiotics. One-stage replacement arthroplasty is a convenient lower cost single procedure and allows early mobility of the patient, however it has higher risk of impairing eradication leading to continued infection from residual organisms. Technically the antibiotic-impregnated cement is used upon re-implantation of new prosthesis. Variable infection control success rate of 70-100% with mean rate of 93% for this treatment has been documented (Becker *et al.*, 2016).

The current usual treatment for chronically infected joint more than four weeks involves a two-stage replacement arthroplasty. It is recommended for treating fungal infection as well. The infected prosthesis is removed and replaced with an antibiotic spacer during initial debridement. Then delayed reconstruction of new implant is performed after a course of parenteral antibiotics for four to six weeks. The interval between the first debridement stage and the second re-implantation stage is typically 6 weeks or longer. Most importantly, the patient must be medically fit for multiple surgeries and affected knee requires adequate bone stock. Confirmation of microbial eradication such as by clinical examination, laboratory blood results of WBC, ESR and CRP, as well as repeat aspiration fluid cultures at least two weeks after planned completion antibiotic course before re-implantation of new prosthesis has been advocated. The success rate of two-stage replacement arthroplasty was slightly lower compared to one-stage exchange arthroplasty. This is because one-stage replacement is selectively performed in patients with less bony defects, low-virulent micro-organisms, and minimal chronic diseases. However statistically there was no significant difference between these two techniques (Becker *et al.*, 2016).

Antibiotic treatment is administered through an intravenous route, depending on the causative bacteria for four to six weeks. Empirical intravenous antibiotics is given after intra-operative fluid aspiration and tissue cultures are taken, commonly first generation cephalosporin i.e. cephalexin. Vancomycin is empirical antibiotics of choice in cases of unidentified initial organism, patients with history of MRSA exposure, or patient who allergic to penicillin. Subsequent parenteral antibiotics regime must be tailored based on microorganism and susceptibility testing. For example, daptomycin is an excellent antibiotic against Staphylococcal biofilms especially in combination with rifampicin. Quinolones are the antibiotics of choice for Gram-negative bacteria.

During the infected prosthesis being explant, surgeon should perform thorough debridement especially bone- implant interface as well as surrounding soft tissues. Then the dead space of knee joint is replaced with antibiotic impregnated cement spacer i.e. vancomycin or tobramycin. Apart from reducing knee joint dead space, the cement spacer provides stability and deliver high dose of local concentration of antibiotics.

Resection arthroplasy is another option of treatment in prosthetic joint infection. Patients who are elderly, non-ambulatory or medically unfit for multiple surgeries are among the candidates for resection arthroplasty. It is also indicated in complicated cases such as in failure of multiple previous re-implantations, presence of recurrent infections with multidrug resistant organisms and patients who have poor bone and soft tissue quality of knee joint secondary to severe infection or surgeries. All infected tissues and implant components are removed without subsequent re-implantation plan. This salvage procedure however gives rise to poor lower limb function, short limb leading to patients' dissatisfaction.

Apart from resection arthroplasty, knee joint arthrodesis can be considered in patients who reimplantation is not feasible due to poor bone stock or patients with recurrent infections with virulent organisms. In rare occasion, when knee infections are recalcitrant to other options of treatment, for example severe soft tissue compromise and bone loss limb, or even vascular damage, sacrificing surgery or transfemoral amputation is the final consideration.

CHAPTER 3

OBJECTIVES

3.1 General Objective

To assess the relevance of intra-operative bacteriology swab culture in primary total knee replacement and risk factors associated with post-operative infection.

3.2 Specific Objectives

1. To determine positive results of intra-operative bacteriology swab culture in primary total knee replacement.
2. To assess the association between post-operative prosthetic joint infection with positive results of intra-operative bacteriology swab culture in primary total knee replacement.
3. To assess the association between risk factors of age, gender, obesity, diabetes mellitus, rheumatoid arthritis, smoking and duration of surgery with post-operation infection.

3.3 Hypothesis

There is a significant prevalence of positive result intra-operative bacteriology swab culture in primary total knee replacement. There is also association between prosthetic joint infections with positive result of intra-operative bacteriology swab culture in primary total knee replacement. Besides, there is significant association between risk factors of age more than 65 years old, male gender, obesity of BMI more than 30kg/m^2, diabetes mellitus, rheumatoid arthritis, smoking habit and prolonged duration of surgery more than 1.9 hours, with post-operative infection.

3.4 Rational of Study

Procedure of obtaining intra-operative bacteriology swab for culture in primary total knee replacement is not routinely practised. In comparison of revision surgeries, it is vital to obtain fluid aspiration and tissues sample for culture and sensitivity. There is no exact recommendation or protocol which suggests to obtain bacteriology swab in primary surgery. Up to this date, not many studies are available discussing regarding this practise and its relevance. Nowadays this procedure is practised in a number of arthroplasty centres based on their preferences.

Their argument of performing this procedure is because even in primary total knee replacement surgery, there is risk of contamination during surgery, particularly from skin of the patient and airborne particles from the theatre personnel (Jonsson *et al.*, 2014), (Byrne *et al.*, 2007). Besides, in immunocompromised patients, for example in rheumatoid arthritis and diabetics, there is also possibility of undiagnosed subclinical knee joint infection present at the time of surgery.

There are many methods of obtaining bacteriology swab culture such as swabbing onto prosthesis surfaces before and after implantation, as well as sampling of knee joint fluid immediately after joint capsule incision and after completion of bone cut surfaces preparation.