Department of Health Science and Technology

The Value of Tourniquet: Implant Fixation and Rehabilitation in Cemented TKA

AALBORG UNIVERSITY
DENMARK

PhD Thesis by
Ashir Ejaz

River Publishers

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You miss 100% of the shots you don't take
Wayne Gretzky

Preface

This thesis is based on scientific work conducted in 2010-2013 during my employment as a clinical research assistant at the Department of Orthopedics, Aalborg University Hospital. At the same time I was enrolled as a PhD student at the Faculty of Medicine, Aalborg University. The clinical work was performed at Department of Orthopedics, Farsoe Hospital, Aalborg University Hospital.

I always thought that writing the acknowledgements would be the easy part of the whole PhD thesis. I was very wrong. In fact, it took me about same time as writing some of the chapters. I also realized it was my chance to tell a bit about my journey getting here. I still remember the day when Poul Torben Nielsen approached me and planted the idea of me doing research and pursuing an academic path before continuing what I love most, the craft of orthopedics. During the last 4 years I have challenged my personal limits in many ways. I have achieved important aims, expanded my horizon socially and scientifically and at the same time, having fun doing so. This would not have been realized without the wonderful people in my life, who believe in me and encourage me to pursue whatever I want to.

I wish to thank my wonderful parents Rukhsana and Ahmed for their unconditional love and support throughout my life. They have always encouraged me of whatever I liked and followed my pursuit of crazy adventures and at the same time keeping me grounded. I will never be able to pay you back. To my dear brother – I always enjoy sharing everything with you in life and cannot thank you enough for being the person I always can count on. It was fun eating a lot of take-away food with you during the writing phase, thanks ;-)

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Also a big thanks to Sten Rasmussen, for guidance into the field of science and writing. For always being supportive and sharing your knowledge. I highly value you as a supervisor. You indeed let me evolve on my own and at the same time guided me.

Andreas Kappel, I sincerely appreciate the patience you had while operating all the patients with me. You indeed are a gifted surgeon who has taught me the importance of immaculate and precise surgery – I will always remember that.
A special debt of gratitude to Thomas Jakobsen, for invaluable help in preparing all manuscripts and the thesis. You spent lot of time with me discussing all aspects, which I am very grateful for. Mogens B. Laursen thank you helping reading manuscripts.

Anders C.Laursen, my scientific partner in crime. Thank you for your friendship and making the PhD years fun. I appreciate your reviews and comments in manuscript preparation.
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I am very grateful to Ulla Hornum and Gitte Broholm for their constant energy and spending lots of hours keeping the study on right track. Also I would like to thank all the excellent nurses and secretaries in Farsoe, without you this study was not possible. A special thanks to Hanne Brink and Birgitte Rusborg for always helping me immediately and with a big smile.
I am very grateful for all the people working at the orthopedic departments in Aalborg and Farsoe. The fact you always asked about my trials and were supportive means a lot to me.

I deeply appreciate my orthopedic colleagues and fellow phD students, you guys are the best. Especially my good friends Janus and Luis, I value all the late nights at the office talking about orthopedics and life!
Rene, you indeed are a good friend and fellow PhD student, thanks for your constant help!
Jens, you´re one of my dearest friends, an excellent surgeon and a companion, which I always appreciate. At the same time always being a person I can depend on. Thank you!

To all of my best friends, THANK YOU!!

In the beginning, I was having thoughts of doing a PhD and one of my friends said: It´s like a big school assignment – just do it!

Finally my PhD is over – yeaahhhh!

Ashir Ejaz
Aalborg 2014

List of papers

This PhD thesis is based on the following papers:

I. The Value of Tourniquet Application in Total Knee Arthroplasty: A Randomized Study of 70 Patients.
Ashir Ejaz, Anders C. Laursen, Andreas Kappel, Mogens B. Laursen, Thomas Jakobsen, Sten Rasmussen, Poul Torben Nielsen.
(Accepted in Acta Orthopaedica 2014)

II. Tourniquet Induced Ischemia and Changes in Metabolism during TKA: A Randomized Study Using Microdialysis.
Ashir Ejaz, Anders C. Laursen , Andreas Kappel, Thomas Jakobsen, Poul Torben Nielsen, Sten Rasmussen.
(Submitted)

III. Absence of a tourniquet does not affect fixation of cemented TKA: a randomized RSA study of 70 patients.
Ashir Ejaz, Anders C. Laursen, Andreas Kappel, Thomas Jakobsen, Sten Rasmussen, Poul Torben Nielsen, Mogens B. Laursen.
(Submitted)

The papers will be referred in the text by their Roman numerals (I-III):

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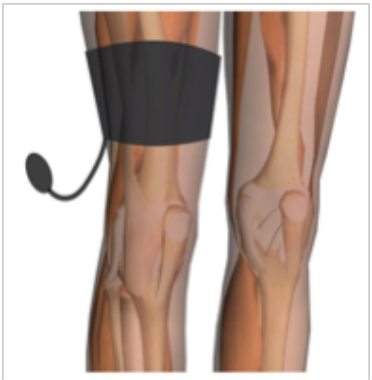
Thesis at a glance

Paper I

Hypothesis: Absence of a tourniquet during TKA improves functional outcomes and rehabilitation by reducing post-operative pain and improving early knee range of motion (ROM).

Design: 70 patients undergoing TKA surgery were randomized into a tourniquet group (n=35) and a non-tourniquet group (n=35). Primary outcomes investigated were functional and clinical outcomes, as evaluated by the Knee Injury and Osteoarthritis Outcome Score (KOOS), and knee ROM.

Results: TKA surgery without a tourniquet results in better functional outcomes and improved knee ROM in the early period of rehabilitation.

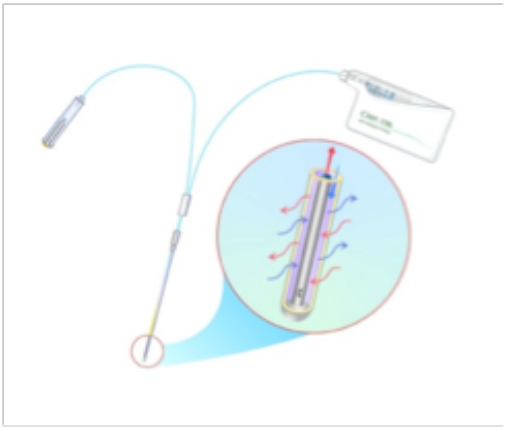


Paper II

Hypothesis: Tourniquet use induces ischemia during TKA surgery and reperfusion.

Design: MiD catheters were inserted in the gastrocnemius muscle of both legs, operated leg and non-operated leg. Interstitial dialysate was collected before and during surgery and at 20 min intervals during a 5 hour reperfusion period. Main variables were metabolites serving as indicators of tissue ischemia.

Results: Using tourniquet is associated with increased ischemia and cell damage, during the first postoperative hours. The changes are reversed after 5 hours.

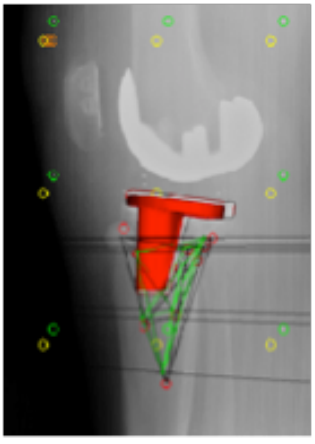


Paper III

Hypothesis: Absence of a tourniquet does not negatively affect the quality of cement-tibial component fixation.

Design: During surgery all patients had tantalum beads inserted into the proximal tibial bone. Using model-based RSA, the migration of the tibial component was analyzed. The follow-up period was 2 years.

Results: The tibial component was well fixated and no difference in migration between the two groups was detected after 2 years, indicating that stable fixation can be achieved without use of a tourniquet.



Abbreviations:

BMD	Bone mineral density
CN	Condition number
CPK	Creatine phosphokinase
KF	Knee flexion
KOOS	Knee Injury and Osteoarthritis Outcome Score
MERBF	Mean error of rigid body fitting
MTPM	Maximum total point motion
MiD	Microdialysis
Non-Tq group	Non tourniquet group
ROM	Range of motion
RSA	Radio stereometric analysis
Tq group	Tourniquet group
TKA	Total knee arthroplasty
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Arthritis Index

Summary in English

Pneumatic tourniquets are widely used in orthopedic extremity surgery. Especially in TKA they have an established place, ensuring surgical overview in a bloodless field and decreasing bleeding. Despite knowing that tourniquet causes ischemia and soft tissue damage surgeons still carry on using them and are often not conscious of the exact extent of ischemia and damage tourniquets can inflict. One of the main reasons for using a tourniquet in TKA is theoretical i.e., assuming that the quality of cementation is enhanced, thereby improving implant fixation.

Studies using RSA have shown early tibial migration is associated with increased risk of short- and long-term revision. Due to the special loading kinematics of the tibial component in the TKA procedure, good cementation is of vital importance, and it is of great concern to surgeons if this is not achieved, especially if a tourniquet has not been used.

The advantages should always be balanced against the risks involved in tourniquet use. The advantages have been considered to include absence of intraoperative bleeding, better surgical overview and concurrently a reduction of surgical time and better cementation of the components. The disadvantages include nerve palsy, vascular and skeletal tissue injuries, severe thigh pain and swelling, and diminished range of motion. Cases of impaired cardio-respiratory function, pulmonary thromboembolism and rhabdomyolysis induced by tourniquet use have all been reported. Due to hypoxia and impaired postoperative tissue perfusion, wound healing disorders and early infections have been attributed to the use of a tourniquet.

The aim of this study was to investigate in a randomized controlled setup, in which patients were allocated to a tourniquet group and a non-tourniquet group, whether the absence of a tourniquet during cemented TKA would affect:

1. The clinical outcomes regarding rehabilitation (KOOS) and knee range of motion
2. The ischemic conditions in soft tissue
3. Implant fixation

Study I investigated the effects of tourniquet use with regard to functional and clinical outcome, evaluated with the use of the Knee Injury and Osteoarthritis Outcome Score (KOOS) and knee range of motion. Secondary outcomes were assessed regarding as perioperative features, postoperative pain and analgesic consumption. In patients in whom a tourniquet was not used, functional outcomes, range of motion and pain, were clearly better in the initial stage and during the first 6 months. Furthermore, no difference in surgical time or surgical visibility was found. Patients operated without a tourniquet had less pain and analgesic consumption postoperatively.

Study II investigated tourniquet-induced ischemia using the technique of microdialysis (MiD). It seems apparent that mechanical compression of the thigh muscle induces local ischemia, whereas very little is known about ischemic changes distal to the cuff. Ischemic metabolites were investigated by placing a microdialysis catheter in the calf muscle of the operated leg and the non-operated leg in both randomization groups. Before surgery and during a reperfusion period of 5 hours, markers of ischemia and cell damage, pyruvate, glucose, lactate and glycerol, were collected and analyzed.

Microdialysis showed that a tourniquet causes significant ischemia and that markers are affected until 3 hours after cuff removal.

Study III investigated the fixation of the tibial component using RSA, which allows in vivo 3-D migration measurements of the implant. Migration was compared between the two groups using the maximum total point motion (MTPM) as primary outcome. Secondary RSA outcome was expressed as translation and rotation along and around the x, y z axes.

After 2 years, no difference could be determined between the two groups in total migration (MTPM) and single direction with regard to translation and rotation. All implants inserted without a tourniquet were stable.

This PhD thesis demonstrates that not using a tourniquet during TKA facilitates initial rehabilitation in terms of better clinical outcomes and reduced ischemic conditions without compromising durable implant fixation or the quality of cementation. These results warrant further trials investigating ischemic conditions and implant fixation.

Summary in Danish

Pneumatisk blodtomhedsmanchet (tourniquet) er hyppigt anvendt ved ortopædkirurgiske indgreb. I særdeleshed anvendes manchetten ved elektiv total knæ alloplastik (TKA), hvor den medvirker til at skabe bedre kirurgisk overblik i et blodtomt felt og mindsker blødningen. Velvidende at tourniquet medfører iskæmi og vævsskade bruges den fortsat af kirurger, uden det nøjagtige omfang af iskæmi graden og vævsskade kendes.
En af hovedårsagerne til brug af tourniquet vedrører kvaliteten af cementering og knogle-cement bindingen, i det blødning kan forringe protesens fiksering.
Det er i studier fastslået, at tidlig migration af tibia komponenten er associeret med øget risiko for tidlig revision. Grundet tibia komponentens specielle belastningskinematik, er bekymringen ved TKA operationer stor, hvis en tilfredsstillende cementering ikke opnås grundet fravær af tourniquet. Fordelene ved tourniquet brug skal altid opvejes i forhold til ulemperne og inkluderer mindre blødning under operationen, bedre oversigt i feltet og dermed mindskes operationstiden. Ulemper er kar- og nervebeskadigelse, vævsskade, smerter og hævelse i lårbensmuskulatur, nedsat bevægeudslag af knæet. Ydermere er der beskrevet svære hjertelunge komplikationer, blodpropper og rhabdomyolyse grundet brug af tourniquet. Grundet hypoxi og nedsat vævsperfusion som skyldes manchetten, er der beskrevet dårlig sårheling og øget infektionsrisiko.
Formålet var at undersøge, i et randomiseret studie, om fraværet af tourniquet ville påvirke

1. Kliniske outcomes vedrørende rehabilitering (KOOS) og bevægeudslag af knæet (ROM)
2. De iskæmiske forhold i skelet muskulatur under og efter operation
3. Protesefikseringen

Studie I undersøger tourniquet´s effekt på funktionelle og kliniske outcome, evalueret med Knee Injury and Osteoarthritis Outcomes Score (KOOS) samt bevægeudslag af knæet. Sekundære outcomes blev undersøgt i form af peroperative data, postoperativ smerte og analgetika forbrug.
Funktionelle outcomes samt bevægeudslag var bedre i den tidlige rehabiliteringsfase ved fraværet af tourniquet og op til 6 måneder, hvorefter forskellen var udlignet. Der var ingen forskel i operationsvarighed og patienter opereret uden tourniquet, havde mindre smerter og mindre brug af analgetika og samtidig ingen behov for postoperative blodtransfusioner.
Studie II undersøger de iskæmiske forhold påført af tourniquet ved brugen af microdialyse (MiD). Den mekaniske kompression af lårbenet synes tydelig, men meget lidt vides om de iskæmiske forhold distalt i ekstremiteten. Iskæmiske metabolitter blev undersøgt ved at isætte et MiD kateter i hver lægmuskel, af henholdsvis det opererede ben og det ikke-opererede, hos begge randomiseringsgrupper. Præ- og postoperativt blev der opsamlet prøver. I løbet af reperfusionsperioden på 5 timer blev der analyseret på pyruvat, glukose, laktat og glycerol. Microdialyse påviste, at tourniquet medfører en betydelig, men reversibel iskæmi med metabolitter, der er påvirket op til 3 timer efter operationen.
Studie III undersøger fikseringen af tibia komponenten ved brug af RSA, der muliggør 3D målinger af protesemigration. Migrationen mellem de to grupper blev undersøgt ved hjælp af maximum total point motion (MTPM) som primær effektmål. Sekundære effektmål blev udtrykt som translation og rotation, hvv. langs- og rundt om x-, y- og z-aksen.
Efter to år er der ingen forskel i migration mellem de to grupper i hverken MTPM eller translationer/rotationer. Alle proteser isat uden brug af tourniquet er stabile.
Denne PhD påviser at fraværet af tourniquet faciliterer en tidligere rehabilitering i form af bedre tidlige kliniske outcomes, nedsat iskæmisk påvirkning af muskulatur og samtidig kompromitteres cementeringen ikke og en god protesefiksering kan opnås. Yderligere studier påkræves, til at undersøge de iskæmiske forhold samt protesefikseringen.

Introduction

TKA is a successful procedure that provides substantial improvement in functional status and pain relief. A total of 8194 TKAs were performed in 2012 in Denmark, 90% of these were cemented and more than 90% of the procedures involved tourniquet use [2]. Even with this success, aseptic loosening continues to be a concern. This emphasizes the need for a thorough investigation that sheds light on the question of whether a tourniquet still has a role in modern knee replacements.

Tourniquet application is widely used in extremity surgery to create a bloodless field and thereby improve surgical visibility. The decision to use a tourniquet should be based on several factors, including considerations of the technical demands of the procedure, the location and duration of the procedure and the estimated blood loss. One of the main reasons for the continuing use of a tourniquet in TKA is that, theoretically, better cementation and adherence between the bone-cement interface are obtained, and this enables a superior implant fixation[3]. A reduced intraoperative blood loss is also among the supposed benefits. With reduced bleeding, the surgical overview is enhanced, enabling a more convenient operation procedure for the surgeon. These factors may reduce surgical time[4].

Disadvantages include a number of risks, including nerve palsy, soft tissue damage to the muscle, postoperative stiffness and swelling due to the compartment syndrome. Cardiorespiratory function can be impaired during inflation and deflation, which can lead to cardiac arrest. Early infections and wound healing disorders due to reduced postoperative tissue perfusion have also been registered [1,5,6].

The characterization of tourniquet-induced ischemia in TKA in vivo has not been investigated before, and therefore very little is known about the metabolic changes during and after surgery.

Two studies have been published that investigated implant fixation when a tourniquet was not used in TKA surgery, both used marker-based RSA[7,8].

To our knowledge this PhD thesis is the first to use microdialysis to investigate ischemia and model-based RSA to evaluate implant migration and fixation in relation to tourniquet use.

Aim

The aim of this thesis was to investigate the value of tourniquet use on early rehabilitation, the extent of ischemia and on implant fixation. Furthermore, the perioperative measurements were assessed to evaluate potential difficulties encountered when performing TKA surgery without tourniquet use. All patients were followed on an out-patient basis for 2 years to monitor the recovery phase.

All the studies were based on in vivo measurements in patients that were randomized into two groups, a control group and an intervention group.

All perioperative data were recorded to evaluate differences between the two groups, with special emphasis on clinical and functional outcomes like pain and range of motion (study I). During surgery, all patients had microdialysis (MiD) catheters inserted into the gastrocnemius muscles of both legs to characterize the ischemic and metabolic changes taking place during surgery (study II).

Model-based radiostereometric analysis (RSA) was used to evaluate the possible migration of the tibial component (study III).

Hypotheses

Study I

Absence of a tourniquet during TKA improves functional outcomes and rehabilitation by reducing postoperative pain and improving early knee range of motion (ROM).

Study II

Tourniquet use induces ischemia during TKA surgery and reperfusion.

Study III

Absence of a tourniquet does not negatively affect the quality of cement - tibial component fixation.

Background

Tourniquet use and application – an overview

Historical perspective

The roots of modern pneumatic tourniquet use can be traced back to the early Roman days (199 BCE –500 CE). In 1718, the French surgeon Jean Louis Petit invented a screw device that could occlude blood flow and called it a tourniquet, derived from the French "tourner," meaning to turn.

Joseph Lister is credited as being the first to use a tourniquet to create a bloodless surgical field in 1864, and he also recommended exsanguination of the limb by elevation before application of the tourniquet.

Friedrich von Esmarch developed a rubber bandage in 1873 that would control both bleeding and exsanguination. This device is known as Esmarch's bandage for surgical hemostasis or Eshmarch's Tourniquet. At that time, this device was superior to Petit's device as there were no screws to loosen or cloth to tear.

In 1904, Harvey Cushing developed the first pneumatic tourniquet. This type of tourniquet compressed the underlying blood vessels using a compressed gas source to inflate a cylindrical bladder. This was superior to the Esmarch tourniquet in two ways: (1) the tourniquet could be applied and removed quickly and (2) it reduced the risk of nerve paralysis[9].

Nowadays the pneumatic tourniquet is widely used in extremity surgery. Gas is used to inflate the cuff to constrict blood flow. Regulating devices on the tourniquet apparatus can be preset to control the amount of cuff pressure exerted on the limb.

Appliance and Design:

The choice of a tourniquet cuff should be individualized, taking into consideration the size and shape of the patient's limb and the specific demands of the operative procedure. Before applying a tourniquet, information about the patient should be obtained regarding coexisting medical conditions, such as cardio-respiratory diseases or peripheral vascular diseases. Such conditions may increase tourniquet-related complications and represent a relative contraindication.

Prior to inflation, the limb is generally exsanguinated. The following median percentages in reduction of blood volumes have been presented [10]: when the lower limb is elevated for 5 seconds, a reduction of 44% occurs, 15 seconds 45%, 30 seconds 46%, 60 seconds 46% and 4 minutes 42%. This indicates that a short elevation is sufficient before cuff inflation.

The pressure beneath the cuff varies widely compared to the pressure in the cuff itself. Tissue pressure decreases progressively from the cuff´s center to the edges, with a 90% decrease. Pressures are also different from surface to deeper tissue layers, but only with a 2% difference. The inverse relationship between limb occlusion pressure and the ratio of cuff width to limb circumference is illustrated in figure 1.[11]

Figure 1 shows that a narrow cuff requires a higher pressure to occlude blood flow. A higher pressure gradient is associated with an increased risk of neurological injury [12].

For the same limb circumference, a wider cuff requires a lower pressure to stop blood flow. Additionally, if a contoured tourniquet is used instead of a cylindrical with the same width, a lower inflation pressure can be used to stop blood flow (fig. 2)[13].

These factors may lead to an awareness of how important a correct cuff fit is, so an efficient transmission of pressure to the underlying tissue is possible. In fact, this has led to the development and increasing use of wide, variable-contour cuffs that adapt to a wide range of limb shapes. These cuffs stop blood flow at even lower pressures compared to cylindrical cuffs.

Tourniquet dating c.1830

Modern pneumatic tourniquet

Occlusion Pressure:

Limb occlusion pressure (LOP) is defined as the minimum pressure required to stop the arterial blood flow in a limb distal to the cuff. To ensure a minimum risk of nerve damage, the tourniquet pressure should be set on the basis of the lowest occlusion pressure. LOP is determined by slowly increasing tourniquet pressure until distal blood flow is stopped, for instance confirmed by Doppler signal elimination.

The tourniquet pressure should be determined by patient's blood pressure and the size and shape of the extremity. Conical curved cuffs that fit the extremity are ideal, since they require less occlusion pressure than straight rectangular ones [14]. Several variables accounts for LOP such as systolic blood pressure, cuff design, application method, thigh shape and circumference. Final cuff pressure is typically set after LOP is determined by adding an additional safety pressure to account for physiologic variations and changes that may occur during surgery.

Earlier recommendations of adding 50-75 mmHg and 100-150 mmHg to systolic blood pressure for upper and lower limb surgery, respectively, may not be an ideal way to determine cuff pressure. Often the pressure is too high and may cause soft tissue and nerve damage. In a 2009 guideline, Recommended Practices for the Use of Pneumatic Tourniquet by the US Association of Registered Perioperative Nurses[15] it was suggested that tourniquet pressure be set by limb occlusion pressure and a margin of 40 mmHg for patients with a systolic blood pressure <130 mmHg, 60mmHg for those of 131-190mmHg and 80 mmHg for those of > 190mmHg.

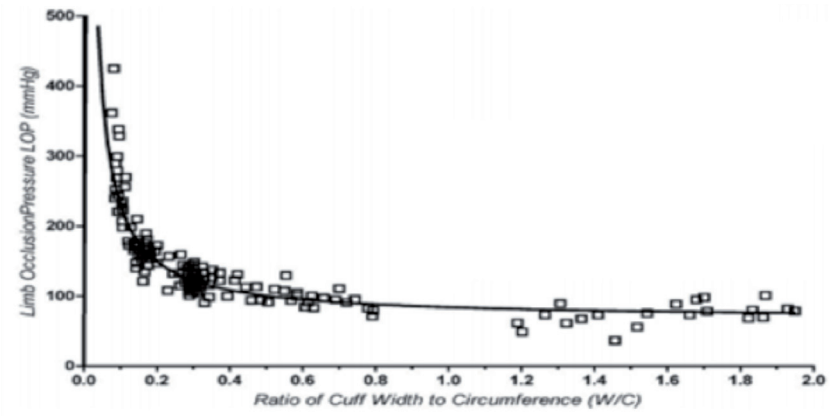


Fig. 1
Limb occlusion pressure vs the ratio of tourniquet width to limb circumference. For any given limb circumference, the tourniquet pressure required to stop arterial blood flow decreases inversely as the width of cuff increases.

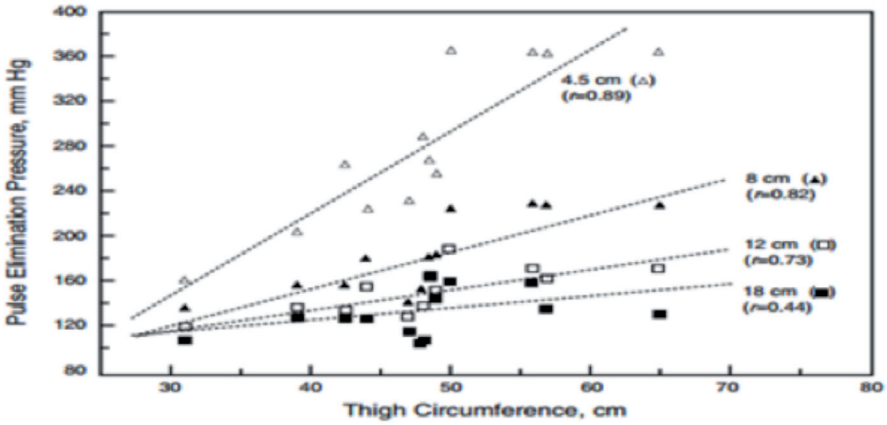


Fig. 2
The relationship between pulse elimination pressure and thigh circumference for four cuff widths. Dashed lines represent a best-fit linear regression corresponding to each width.

Duration of tourniquet application

Complications due to tourniquet use increase as tourniquet time increases. A 2-hour tourniquet period is considered relatively safe for upper limb surgery [16, 17]. Serum creatine phosphokinase (CPK) is elevated in response to muscle damage and has been used as a marker of safe application times [18]. In canine studies there is no CPK elevation after 1 hour, but there was an elevation after 2-3 hours application [19, 20]. These findings are consistent with what Östman et al. (2004) found using microdialysis in a clinical setting to characterize metabolites in skeletal muscle subjected to ischemia during arthroscopic ligament reconstruction. The ischemic changes were restored after 2 hours of tourniquet deflation.

One method to "prepare" the skeletal muscle is preconditioning, whereby the muscle is subjected to a short time of ischemia followed by reperfusion before the longer periods of ischemia. In this way a replenishment of energy is allowed, and at the same time the elimination of toxic metabolites is facilitated. The method has successfully been used in cardiac surgery to protect the myocardium [22].

Tourniquet deflation

After the tourniquet is deflated and removed, monitoring of the patient is necessary because several complications can occur. Pulmonary embolism, due to deep vein thrombosis, can occur suddenly after release of tourniquet pressure, but the tourniquet may not be the sole cause. In hip and knee surgery, intramedullary bone preparation and cementation are other risk factors that may lead to embolism.

Another phenomena occurring after cuff deflation is "myonephropathic metabolic syndrome", where the return of toxic metabolites creates a systemic metabolic dysfunction. This is characterized by metabolic acidosis, hyperkalemia, myoglobinemia, myoglobinuria, and renal failure [23]. Hyperkalemia because of elevated interstitial potassium due to loss of ion gradients across the cell membrane of ischemic myocytes creates potassium leakage. Concurrently rhabdomyolysis may release myoglobin and intracellular enzymes (CPK, lactic acid and glutamic-oxaloacetic transaminase).

Cuff release prior to wound closure in TKA is associated with greater bleeding and transfusion requirements, and it is suggested that cuff release be done after wound closure, affording a more controllable bleeding [24].

Tourniquet-related complications

Complications include thigh pain, nerve palsy, ischemia, soft tissue damage, thromboembolic complications, poor wound healing and patella maltracking [5, 25, 27, 28]. Although rare, rhabdomyolysis and subcutaneous fat necrosis have been reported [29, 30]. Severe conditions such as altered cardio respiratory status may also be associated with tourniquet use [6, 26].

In TKA surgery, recovery may be delayed due to reduced muscle strength, reduced knee range of motion (ROM) and increased pain [31]. When patients are discharged from acute care, these outcome measurements are often used as a benchmark of how successful initial total knee replacement has been.

Other studies have shown increased pain and impaired knee range of motion up to 1 year after surgery in which a tourniquet was used [1,7]. Several randomized controlled trails and meta-analyses dealing with adverse effects of tourniquet use in TKA have been published, but disagreement regarding tourniquet use still remains [5, 28].

The kinetics of ischemic metabolites during periods of ischemia and reperfusion remains uncertain. The effect of tourniquet pressure combined with ischemia has been investigated, and this combination inflicts a more profound damage to the skeletal muscle than ischemia alone [32].

The skeletal muscle in limbs is very sensitive to ischemic changes, and a clinical assessment is not sufficient [33, 34].

Implant fixation

Total knee arthroplasty (TKA) has become a well-established operative treatment of degenerative knee conditions. The results of TKA have improved in the last decades. Reported survival rates of TKA have reached 95% at 10 years. These results have been achieved by improved surgical techniques as well as the development of implant designs [2] (fig. 3).

Cementing technique is one of the factors that play an important role in this aspect. The technique of cementation in TKA has evolved over the last decade, including pulse lavage followed by suction of the bony cut surfaces and pressurization.

Early and long-term aseptic loosening remains a major cause of failure in TKA and composes 30% of the reasons for revision [2] (fig. 4). Attention has been focused on debris wear, alignment, tibial bone quality and activity level. Therefore, good fixation of the tibial component is a prerequisite to achieving long-term survival of the implant [35].

The diminished bleeding should in combination with the careful pulse lavage provide a deeper cement penetration and better bone-cement bond. This seems to be one of the predominant reasons for the continuing use of a tourniquet.

Although many studies have been performed to settle the question of whether or not to use a tourniquet, they primarily focused on clinical outcomes such as operation time, intraoperative bleeding, pain and knee flexion [1, 26, 38]. Systematic reviews and meta-analysis dealing with the problems of tourniquet use in TKA have not reached a definitive consensus, but encourage that implant fixation should be investigated further [5, 6, 28].

Two studies registered whether loosening, estimated by plain radiographs, had taken place when a tourniquet was not used. [1, 38.]

To avoid waiting for long-term follow-up with plain radiographs, roentgen stereo metric analysis (RSA) can be performed to evaluate early migration with high accuracy [35, 39]. An early migration of the implant is associated with a later loosening [35, 40].

To our knowledge, thorough implant fixation evaluated by RSA has only been carried out in two recent RCT studies, both using marker-based RSA [7, 8]. They supported each other's findings and show that absence of tourniquet did not affect the quality of fixation in cemented TKA.

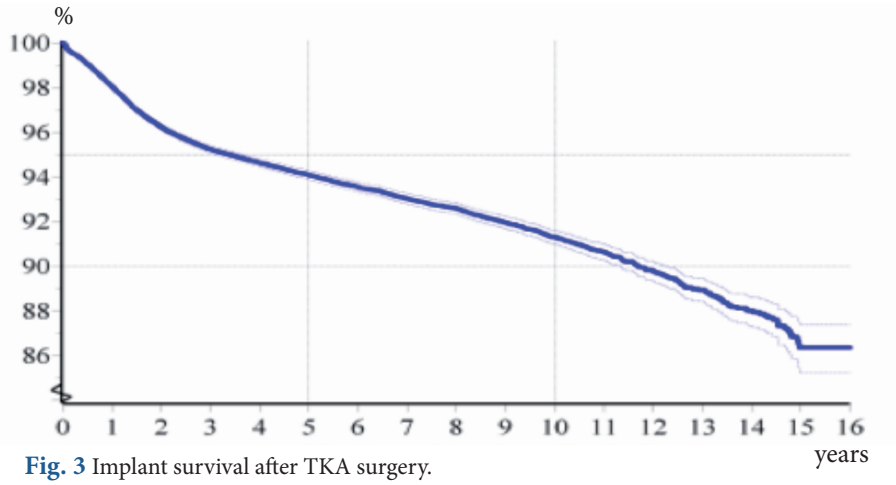


Fig. 3 Implant survival after TKA surgery.

Fig. 4 Major reasons for revision.

Current status of tourniquet use in knee surgery

A total of 8194 TKAs were performed in 2012 in Denmark and tourniquet was used in 90% of the cases when performing cemented TKA surgery [2].

In a meta-analysis and systematic review concerning tourniquet application in TKA several outcomes such as total blood loss, intraoperative blood loss, need for transfusion, operation time, range of motion and complications were investigated [6]. It showed that use of a tourniquet reduced intraoperative blood loss but did not influence total blood loss or need for transfusions. Furthermore there was no difference in surgical time and but increased complications in terms of nerve palsy, DVT and wound healing disorders when a tourniquet was used. These findings were further supported by a meta-analysis by Tai 2011 [28].

Another systematic review and meta-analysis assessing tourniquet use in TKA found that intraoperative blood loss was decreased when using tourniquet but without affecting surgical time [6]. The total blood loss in this study was greater when not using a tourniquet but postoperative bleeding as judged by drain volumes showed no difference. The complication rate was increased when using a tourniquet.

Knee flexion was reported to be better initially when not using a tourniquet, this could be caused by less mechanical compression of the soft tissue of the thigh. Long-term flexion showed no difference.

In arthroscopic surgery tourniquet use has also been investigated. In a RCT by Johnson et al. (2000) the effects of tourniquet use was investigated in 109 patients undergoing knee arthroscopy with or without tourniquet use. No significant difference was found between the two groups with respect to operation time or visibility, postoperative pain score, analgesic use and complications. It was advocated that knee arthroscopy could adequately be done without tourniquet application in order to avoid known risks [71].

Kirkly et al. (2000) investigated 120 knee arthroscopy patients in a RCT and found no difference in functional outcome measured with WOMAC and operation time. However increased pain was registered when using tourniquet for more than 30 minutes and decreased isokinetic strength testing. It was concluded that tourniquet could be used if not exceeding 30 minutes of operation time [72].

This was supported by Tsarouhas et al. (2012) that suggested knee arthroscopy with tourniquet application was safe if kept less than 30 minutes. No difference was found in operation time, postoperative pain score and knee ROM [41].

In comparison with TKA, arthroscopic surgery is less invasive and together with often shorter operation time and younger patient groups, tourniquet use seem more tolerable.

A recent RCT study revealed that limited use of a tourniquet in TKA was preferable during the cementation phase only [73]. Furthermore, no difference in surgical time or blood loss was found, and it was concluded that only applying a tourniquet during the cementation phase was a safe method. The RCT performed by Kvederas et al. (2013) also suggested limited use of a tourniquet during cementation[74].

Although several random control trails and meta-analyses dealing with adverse effects of tourniquet use in TKA have been published, disagreement regarding tourniquet use still remains [5, 6, 28].

In conclusion, performing TKA without a tourniquet may be safe and potential complications can be avoided. At the same time, early mobilization is obtained and eliminating tourniquet use might be a part of fast track surgery to facilitate recovery [42].

Patients and Methodological Considerations

The questions concerning tourniquet use in this thesis arose from clinical practice.

We intended the results to be transferable to clinical practice, and therefore all measurements were conducted in vivo in a standardized way close to the everyday surgical procedures.

A total of 70 primary TKA were included in the prospective randomized clinical trial and performed between January 2011 and January 2012. Approval from the local Ethics Committee (approval no. N-20090045) and registration at ClinicalTrials.gov (NCT01309035) were obtained. All patients gave written consent and were enrolled in this study in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and The Helsinki Declaration.

Patients

Patients aged 50–85 were included if elective unilateral TKA because of gonarthrosis stage 3–5 according to Ahlbäck (1968) was required [43]. All patients were without other severe disease and classified according to the American Society of Anesthesiologists ASA 1-2.

Exclusion criteria included rheumatoid arthritis, peripheral vascular disease, diabetes, prior major knee surgery, BMI ≥ 35 and use of anticoagulation medicine.

Patients were comparable regarding demographics. They were allocated into two groups: surgery using a tourniquet and surgery without the use of a tourniquet.

Patients were block randomized using sealed envelopes. In the operating theater before surgery, the envelope was opened when the surgeon was present. Patients were unaware of the group to which they were allocated.

Limitations

Patients assessed in this study were selected if inclusion criteria were met, thereby excluding patients with severe diseases (ASA 3-4) and peripheral vascular diseases. Thus patients included were, except for their degenerative knee conditions, healthy subjects. Non-use of a tourniquet in patients with impaired cardio-respiratory circulation or using anticoagulation medicine could result in difficulties in the handling of bleeding during surgery. All patients included were eligible to receive tranexamic acid, which often may be contraindicated in some patient group. Excessive bleeding may hinder the bone-cement bond and thereby result in a compromised implant fixation and furthermore compromise surgical visibility.

One experienced surgeon performed all the TKA procedures, decreasing the inter-surgeon variability but at the same time limiting the external validity.

Functional and clinical outcomes

Primary outcomes

To evaluate clinical outcomes, The Knee injury and Osteoarthritis Outcome Score (KOOS) was used [57]. This a validated knee-specific self-administered questionnaire with 42-item assessing pain (9 items), symptoms (7 items), activities of daily living (ADL, 17 items), sports and recreation function (5 items) and knee-related quality of life (QOL, 4 items) in five separate subscales. Each item is responded to by marking one of five response options on a Likert scale. A score from 0 (extreme problems) to 100 (no problems at all) is calculated separately for each subscale.

KOOS was developed for younger and more active people with knee injury and osteoarthritis, but has been found to be a useful, valid and reliable instrument in assessment of outcomes in elderly patients with advanced osteoarthritis [58].

Knee range of motion (ROM) is an important measurement of TKA surgery that determines how successful the operation was. Knee ROM was measured by extension and flexion with a goniometer 2 weeks preoperatively as a baseline, postoperatively on day 2 and during follow-up (8 weeks, 6 months and 12 months).

Secondary outcomes:

Pain was assessed using a VAS score with no distinction between thigh pain and knee pain. Zero was no pain and 10 was worst imaginable pain. Pain was registered at rest, just prior to surgery and postoperatively at 2,4,6,8 and 10 hours on the day of surgery (day 0). The following days, pain was evaluated during rest and after walking 20 meters. Analgesic consumption was expressed as a mean morphine equivalent during hospitalization, and the consumption was standardized using 10 mg of morphine as reference analgesic dose.

Surgical data were recorded regarding blood loss, measured by totaling fluid volume in suction bottles and the weight of operation swabs. The hospital's transfusion policy was followed regarding transfusion needs, and patients were transfused postoperatively if the hemoglobin level was 4.5 mmol/l or lower. Surgical time and surgical visibility were registered by the surgeon using the scale in Table 2.

No problems	1
Slight problems	2
Moderate problems	3
Severe problems	4
Extreme problems	5

Table 2. Surgical visibility.

The Microdialysis technique

Microdialysis is an in vivo sampling technique originally used in neurosurgical research [44, 45]. MiD offers a unique technique that allows monitoring metabolic changes during ischemia and reperfusion in tissue. No studies regarding the tourniquet-induced ischemic changes during TKA have previously been published. We applied this method to investigate the degree of tourniquet-induced ischemia, with special attention to the skeletal muscle.

The principle of microdialysis

The basic idea is to mimic the passive function of a capillary blood vessel. A semipermeable tubular dialysis membrane is inserted into the tissue of interest. The catheter is perfused with a solvent which equilibrates with the surrounding fluid outside the membrane by diffusion in both directions (Fig 5). Because of ion gradients, low molecular weight compounds can diffuse into and out of the probe lumen, whereas larger molecules such as proteins or molecules bound to protein cannot pass the membrane and are excluded. The diffusion coefficient of an analyte determines the migration of the solution. The solution leaving the probe, termed the dialysate, is collected for analysis. Samples obtained represent a local profile of the current metabolic status in the examined tissue. The ratio between the concentration in the extracellular fluid and in the dialysate is defined as relative recovery and is inversely proportional to the recovery rate.

In vivo recovery depends on several factors like membrane length, flow rate, blood flow, speed of diffusion and physiological processes. Recovery remains constant as long as the perfusion rate remains constant. In this study we were not interested in the exact recovery, but the changes over time between two groups. The relative recovery was found sufficient, since at low perfusion rates recovery is close to 100% (fig. 6)[46].

Microdialysis system and application

The MiD system consists of a catheter, a syringe-pump, sampling vials and a dialysate analyzing system. We used a concentric tube, into which the perfusate solution is pumped through the inner tube to the catheter tip. Then transportation upwards occurs between the inner cannula and the membrane and reaches the actual site of dialysis. The dialysate is collected in microvials which can be inserted directly into the microdialysis analyzer, ISCUS.

Although minimally invasive, inserting the catheter causes a very small local tissue lesion. This may affect metabolites of interest, but this local inflammation seems to normalize within 1 hour.

Syringe pumps deliver an accurate perfusate using a constant flow rate of 0.3µl/min

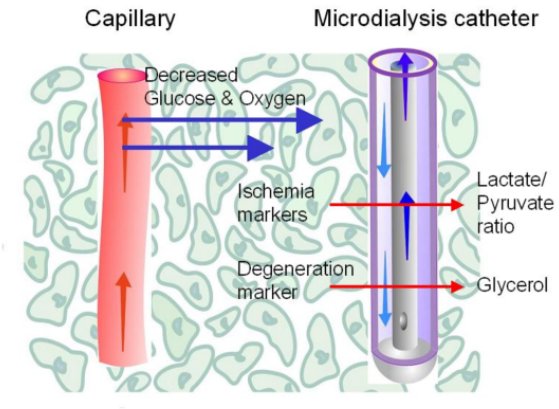


Fig. 5 The basic principle is to mimic the function of a capillary blood vessel by perfusing a thin dialysis tube implanted into the tissue with a physiological liquid. The perfusate reflects the composition of the extracellular fluid with time due to the diffusion of substances back and forth over the membrane.

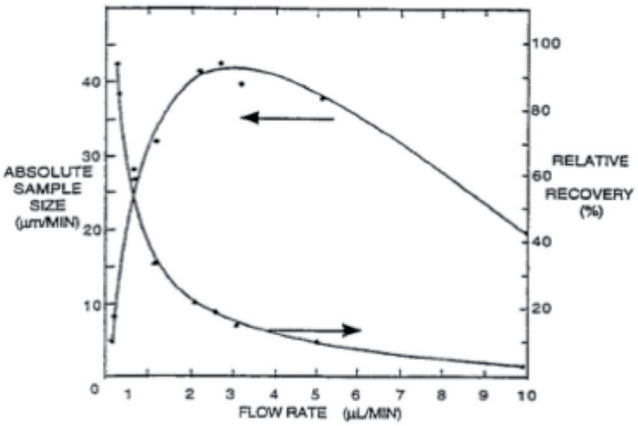


Fig. 6 Relative recovery is inversely related to perfusion flow rate, approaching 100% as the flow rate approaches zero. It decreases as the flow rate increases. Absolute recovery is the total amount of substance collected from the probe during a given time. It is zero when the flow is stopped and increases as the flow increases.

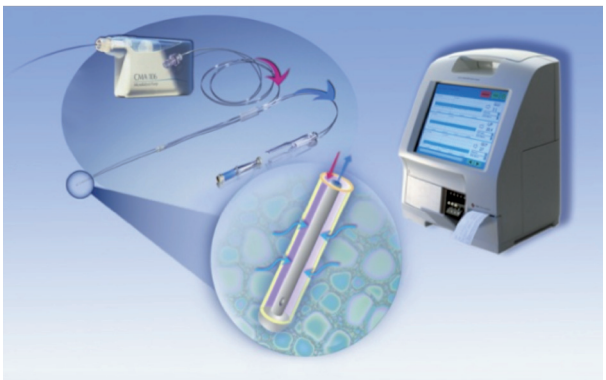


Fig. 7 Third generation Microdialysis Analyzer, ISCUS analyzer with automatic calibration.

The CMA ISCUS is a clinical chemistry analyzer that uses enzymatic reagents and calorimetric measurements (Fig. 7). The reagents oxidize the substrates, and a formation of colometric substance is created, which is measured photometrically as a change of absorbance at 540 nm wavelength
When analyzing glucose, lactate, pyruvate and glycerol, the substrate-specific reagent set was used (Reagent Set A, Solna Sweden).
The temperature in the operation room was set at 19 degrees Celsius at all times.

Microdialysis is an in vivo technique that has been used in several settings to evaluate the interstitial metabolism in different tissues. It represents an opportunity to observe living tissue directly. The microdialysis catheter consists of a double-lumen linear tube that at the tip has a semipermeable membrane, the tube mimics the functions of a capillary blood vessel. The catheter is connected to a pump that, with a constant flow, pumps the fluid so it can pass the membrane. In the interstitial space, diffusion along the concentration gradient and equilibrium takes place, between the fluid and molecules. The molecules are collected in small vials that reflect the composition of the extracellular fluid and can then be analyzed immediately. The metabolites of interests have traditionally been pyruvate, glucose, lactate and glycerol. The lactate/pyruvate ratio was calculated. It increases during ischemia and is a precise marker [75, 76].

In this study we used CMA 60 (CMA Microdialysis AB, Solna, Sweden) catheters (length 30mm, outer diameter 0.6mm and molecular cut off 20 kDa) in skeletal muscle of the lower extremity. In both groups 2-3 ml lidocaine was injected subcutaneously in the gastrocnemius muscles (vastus medialis) then catheters were inserted parallel to the muscle fibers at an angle of 35°. The correct position of the catheter was verified by ultrasonography. In the non-operated leg (reference leg), a catheter serving as a control was inserted at the same level. Catheters were connected to a syringe filled with 4 mL perfusion fluid T1 (CMA Microdialysis AB, Sweden) placed in CMA 106 MD pumps, constantly perfused at a rate 0.3 µl/min. Afterwards a period of 40 min of flushing and stabilization was allowed.
The ISCUS MD analyzer (CMA Microdialysis AB, Solna, Sweden) with Reagent Set A was used to analyze all the collected MiD samples and this was done immediately after sampling.

Microdialysis considerations and limitations

Microdialysates are very dilute solutions and are typically collected in small volumes. This presents a considerable challenge as recovery is only relative, thus the necessity for correct calibration.
The perfusion fluid is continuously flowing through the probe and the concentration of the dialysate will not be in equilibrium with the concentration of the periprobe fluid. Thus, the concentration of the analyte in the dialysate represents only a fraction of its actual concentration in the extracellular fluid which is examined [77, 78]. This limitation, however, does not constitute a major problem during this study because the aim is to detect alterations in ischemic markers over time and not estimate the precise level in the tissue.
The microdialysis technique contains a limit regarding the recovery of larger molecules since it depends of the molecular cut-off of the membrane, we did not investigate large molecules and the membrane used had a cut-off at 20 kDa thereby not creating any difficulties in this study.
When inserting a MiD probe into the tissue, a small amount of tissue damage occurs that lasts up to few hours before normal baseline levels are restored [79, 80]. Glycerol is a component of the cell plasma membrane and is released into the interstitial space when tissue is damaged, for instance, during surgery. But in addition, high levels of glycerol also may be due to the hormonal regulation of lipolysis and hypoglycemia during tourniquet use, and this facilitates a catecholamine response that induces a lipolytic reaction in skeletal muscle [47].
Microdialysis also contains a limitation when estimating data because only approximations can be stated. Recovery is dependent on many factors that affect the equilibrium, but to achieve the best recovery, we used the largest membrane recommend for skeletal muscle and the lowest perfusion rate possible. Most of the clinical studies published use relative recovery [34, 21, 81].
The MiD method must be highly sensitive in order to detect diluted levels of the chosen markers, especially the method should be capable of analyzing the markers in the small volumes generated by the MiD technique. The problem often develops when low perfusion rates are chosen in order to optimize recovery of very small volume samples. On the other hand, high perfusion rates will produce more diluted samples that require even more sensitive analytical methods. Using a constant flow rate of 0.3 µL/min a recovery of nearly 100% was reached.

Advantages	Disadvantages
Collection of substance on the site of action	Low recovery
Continuous sampling	Careful calibration necessary as recovery is relative
Minimal invasive	Risk of tissue damage
	Careful calibration

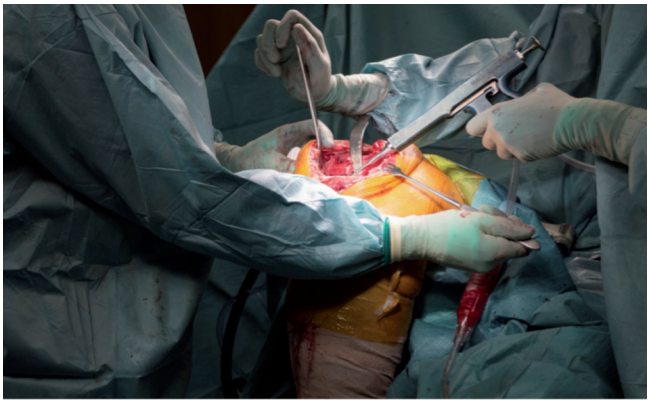
RSA

Basic principles

RSA is a highly accurate method to measure micromotions of joint implants. It was introduced by Selvik and has been used in many different clinical settings since the introduction of arthroplasties [48].

Small biocompatible spherical tantalum beads serving as markers are inserted into the bone region of interest. These markers are projected in radiographs which, in combination with a calibration cage, define a coordinate system that enables calculation of a 3-dimensional coordinate. A minimum of three non-linear coordinates is required to form a rigid body representing a segment, i.e. an implant or a bone. With this technique the migration between two rigid bodies can be detected between two examinations. Migration represents gradual motion over time and is the relative motion between two examinations performed at different time points (Picture 2).

In our study, 14–16 spherical tantalum beads of 1.0 mm were placed in the proximal tibia before inserting the implant. They were carefully scattered in all directions so that a suitable rigid body could be formed (picture 1).



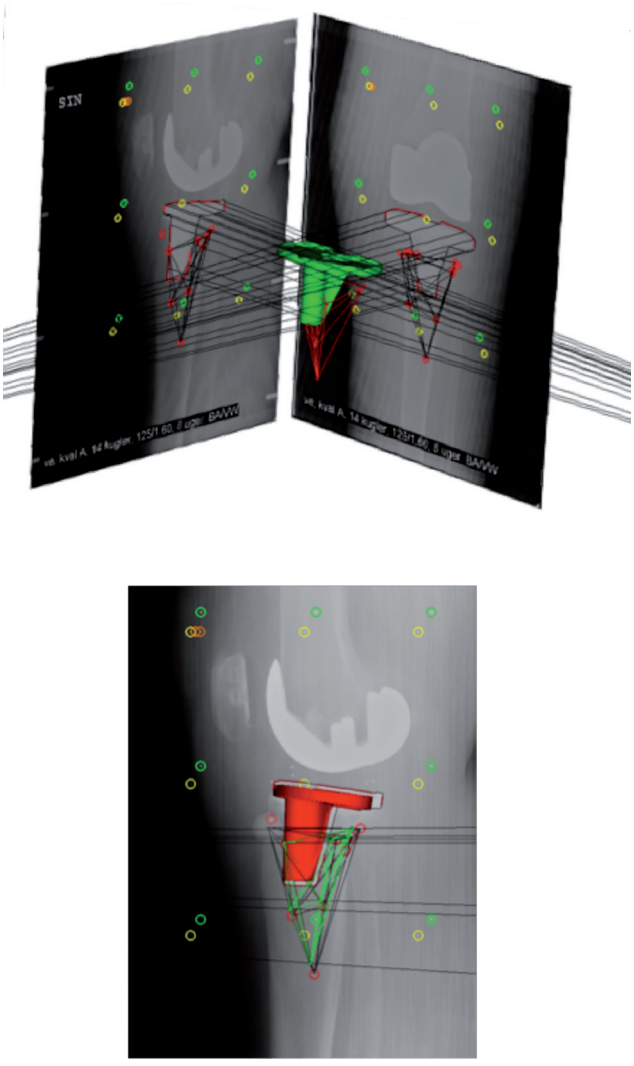
Picture 1. Securing a proper scattering of the tantalum markers in all directions, to create a 3-D rigid body.

RSA examinations were all performed at Farsoe hospital where a RSA setup is available. Examinations performed were as follows:

- First postoperative day, used as reference examination
- 2 month follow-up examination
- 6 month follow-up examination
- 12 month follow-up examination and here double examinations were performed with total repositioning of the patient and the radiographic equipment
- 24 month follow-up examination

The RSA setup was as recommended in Valstar et al. (2005) [49], with two ceiling-fixed automatically synchronized roentgen tubes, which were angled 90^0 relative to each other (Picture 3). A biplanar calibration box (Lund Knee box, RSA Biomedical, Sweden) was placed in the midsection of the roentgen focus (picture 4).

All radiographs were fully digitalized. Precision was evaluated at 1-year follow-up by double examinations, including total repositioning of the patient and the radiographic equipment. All radiostereographs were analyzed using model-based RSA software (MBRSA v3.3.2, Medis Specials, Leiden, the Netherlands) (picture 2).



Picture 2. Model Based RSA: a model of the implant is matched on the radiostereometric picture of the patient's implant. The migration of the implant is determined in relation to tantalum bone markers which are placed in the bone during the operation.

RSA body configuration and stability

For accurate assessment of micromotion, it is crucial that configuration of the rigid body is precise and stable. This means that the tantalum markers should be well scattered in a non-linear fashion in all three dimension and afterwards stay fixated in the same position.

The mean error of rigid body fitting (MERBF) indicates the stability of markers. The mean condition number (CN) indicates the distribution of bone markers and thereby the quality of the rigid body formed by the markers. A low CN indicates a high good distribution and good quality, and it is suggested by guidelines by Valstar et al. (2005) that a CN lower than 90–100 is appropriate and that MERBF be lower than 0.25.[49]

RSA parameters

The main outcome measurement was based on maximum total point motion (MTPM), which represents the vector length of a marker in the rigid body that has the longest translational motion, not considering direction, and always has a positive value. In addition, translations and rotations were calculated accordingly to the standards suggested by Valstar et al. (2005) [49] as secondary RSA outcome variables. Rigid-body translations and rotations of the implant were calculated about a coordinate system centered at the center of the implant, and the axes were aligned with the anatomical directions.

Translations along the axes were given as x-translation (medial-lateral movement), y-translations (superior/lift-off and inferior/subsidence movement) and z-translations (anterior and posterior movements). Rotations around the axes were expressed as x-rotation, y-rotation and z-rotation, which represent anterior-posterior tilt, internal-external rotation and varus-valgus tilt, respectively.

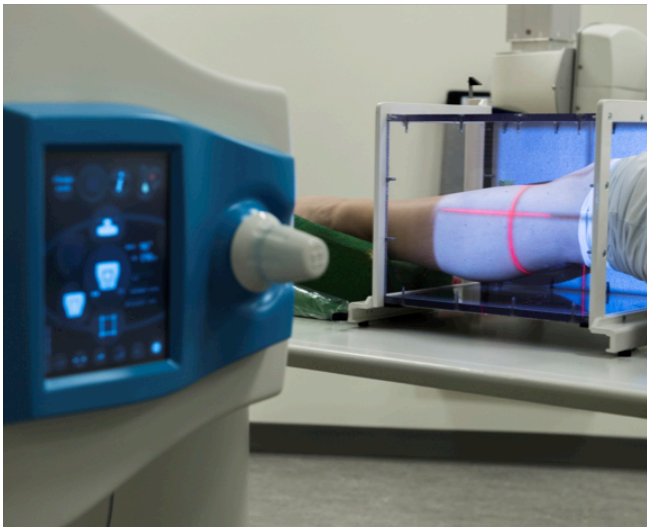
Ryd et al. (1995)[35] categorized implants movements to be stable if MTPM was < 0.2 mm between 1 and 2 years or as being at risk of loosening if MTPM was > 0.2 mm. An accuracy of 0.2 mm for translation and 0.5 degrees for rotations were given by double-examinations. Other studies have reported accuracies that range from 0.05 to 0.5 mm for translation and 0.15° to 1.15° for rotations [50,51].

RSA considerations

One shortcoming of this study was the use of modelbased-RSA from CAD models. The precision relies on obtaining an exact contour detection of the tibial tray geometry. The method has been proven to be a highly accurate method to evaluate fixation of tibial components [52,53]. Other factors such as osteoporosis that can cause motion were not considered in the present study, but randomization should equalize these parameters.

MTPM can easily be affected by movements from all directions, but it is appropriate for detecting differences between two similar groups. Translations and rotations are more precise variables of the rigid body's center of gravity. The MTPM reported in our study is close to the limit for acceptable migration. This limit varies for implant types, because some have more migration than others [54].

Picture 3. The Adora RSA setup: Adora RSA has two X-ray tubes along with two detectors plus a smaller size detector.



Picture 4. Positioning the knee in the center of the two roentgen foci.

Surgical technique

All procedures were standardized with regards to administration of preoperative tranexamic acid, spinal anesthesia, postoperative pain treatment and rehabilitation.

Before surgery, tranexamic acid (1 g) was administered orally, and immediately prior to skin incision, cefuroxime (1.5 g) was administered intravenously. In addition, tranexamic acid (0.5 g) was given 3 hours after surgery, and cefuroxime (750 mg) was given 6 and 12 hours postoperatively. Thrombosis prophylaxis was achieved with use of rivaroxaban (10 mg) throughout hospitalization.

Both groups had an appropriately sized thigh tourniquet applied, but it was only inflated in the Tq group. In non-Tq group, it was placed on the thigh but not inflated, thereby serving as safety device in case of uncontrollable bleeding. In the Tq group, limb exsanguination was done by elevation for 2 min, and the cuff was inflated to 250 mmHg just prior to skin incision.

All knee implants were the NexGen® CR-Flex Fixed Bearing Knee (Zimmer, Warsaw, Indiana, USA) with use of Biomet Refobacin® Bone Cement R (Biomet, Warsaw, Indiana, USA). In all cases, the patella was resurfaced. Surgical procedures were all performed by one single surgeon. A midline skin incision and medial parapatellar arthrotomy were applied. An intramedullary guide system was used for the femur and external guides for the tibia. The distal femur guide hole was plugged with autogenous bone grafts. Cement was applied on the tibia plateau surface, beneath the tibial tray and along the stem. Anchorage holes were drilled into the tibia plateau if necessary, to increase the contact area between bone and cement. The proximal tibia bone was prepared for RSA with the insertion of 14–16 tantalum beads of 1.0-mm.

The corner stones of modern cementing technique are surface preparation including comprehensive high pressure pulse lavage that allows a deeper cement penetration, thereby enhancing the mechanical bone- cement bond by removing blood, fat, bone and cement debris [36, 37]. Careful cleaning of the remaining debris is crucial as it may prevent "third body wear" responsible for polyethylene wear and implant loosening [55] (picture 5).

A common practice is to cement the components in one phase, instead we performed a two-stage cementation procedure. The tibia and patella were implanted first, and then another package of cement was used to fixate the femoral component. This prolonged the operation time, but was done to secure enough time to obtain a careful cementation with proper pressurization. After cementation, further pulse lavage debridement was performed to eliminate cement debris from the wound [56]. Immediately after wound closure, dressings were applied, and the cuff was deflated in the Tq group and removed.

Statistical analysis

Study I

Sample size for this study was based in part on the KOOS score [57] and in part on earlier studies with knee ROM and surgery with and without a tourniquet [7, 59]. A change of minimum 10 points was considered clinically significant. Data as KOOS, VAS pain and other continuous variables that was normally distributed were analyzed with Student's t-test (unpaired). Mann Whitney U-test was used for continuous variables not normally distributed. The chi-squared test was used to analyze categorical variables.

Study II

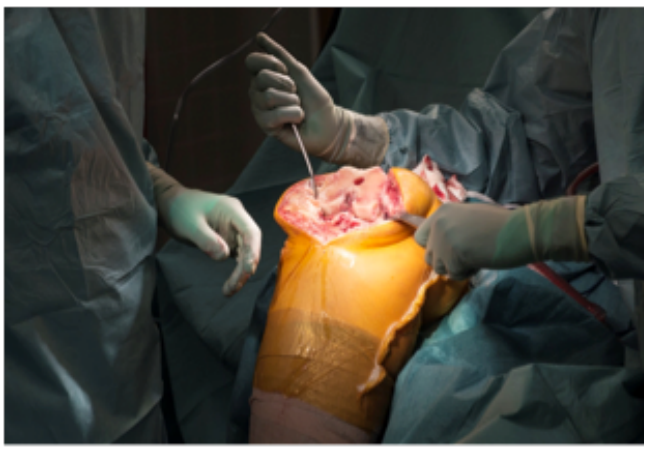
Data for each metabolite over time in each group were analyzed by using analysis of variance (ANOVA), Student´s t-test for comparison of the Tq-group with the non-Tq group, and Wilcoxon rank sum test if assumptions for the t-test were not fulfilled. The metabolic changes during surgery and reperfusion are expressed in percentages of baseline values.

Study III

Sample size was based on earlier studies [7, 60] .Using a SD 0.2 mm with $\alpha = 5$ and $\beta = 80\%$, the sample size of each group was 18. Because of the possible risk of patient drop-out, the number was increased to 35 per group.

In a systematic review, it was suggested that a MTPM migration threshold of less than 0.54 mm was acceptable [62].We chose migration ≥0.5mm in magnitude at 2-year follow-up to be "clinically relevant" based on previous clinical studies [18, 50, 61]. This means the 2SD would have to be within +/- 0.5mm. Data were analyzed with ANOVA and the Mann-Whitney U-test to compare mean difference in migration where appropriate.

The level of significance was set at 95% confidence limit, and a p-value less than 0.05 was considered significant. Data are presented as means and standard deviations. Statistical analysis was performed by using STATA 11.0



Picture 5. Surgical overview after high pressure pulse lavage (tourniquet absent)

Results – summary of papers

Study I

Hypotheses

Absence of a tourniquet during TKA improves functional outcomes and rehabilitation by reducing postoperative pain and improving early knee ROM.

Primary outcomes

Figure 8 shows that both groups had improvement within all KOOS subscales, from baseline until 8 weeks. Differences between groups were also registered, and there was more improvement in the non-Tq group ($p < 0.001$)

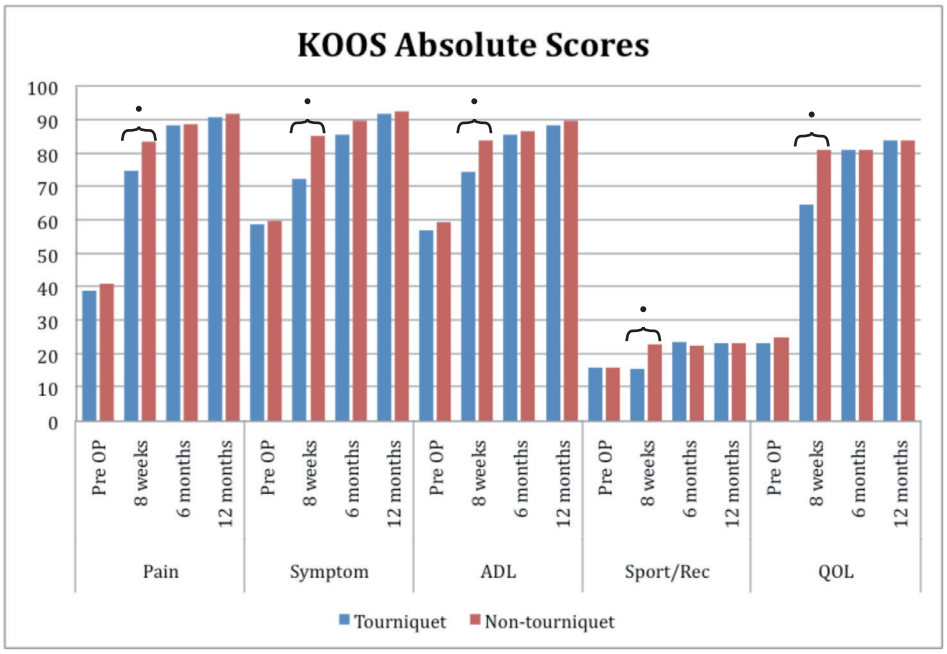


Fig. 8
Absolute mean KOOS subscales are presented at baseline and through follow-up as an outcome profile for the tourniquet group vs. the non-tourniquet group. KOOS subscales: pain, symptoms, activity in daily living (ADL), sport and recreation (Sport/Rec) and quality of life (QOL). Early improvement at week 8 was detected in all KOOS subscales. Statistical significant difference marked with •

Changes from pre OP		Tourniquet			No tourniquet			
		Mean	SD	95% CI	Mean	SD	95% CI	p-value
Pain	Pre OP	38.9	6.0	36.8-40.9	41.1	4.0	39.7-42.5	0.075
	8 weeks	36.0	13.2	31.5-40.6	42.6	9.6	39.3-45.8	0.021
	6 months	49.7	7.9	47.0-52.5	47.8	7.8	45.1-50.5	0.304
	12 months	52.1	7.3	49.6-54.6	51.0	6.8	48.7-53.4	0.542
Symptom	Pre OP	58.8	7.9	56.1-61.5	60.0	7.0	57.6-62.4	0.505
	8 weeks	13.7	12.8	9.3-18.1	25.2	8.9	22.2-28.3	<0.001
	6 months	27.0	8.9	23.9-30.1	29.9	6.5	27.7-32.2	0.120
	12 months	33.1	7.5	30.5-35.7	32.7	7.3	30.2-35.2	0.819
ADL	Pre OP	57.5	4.5	55.4-58.6	59.4	4.4	57.8-61.0	0.062
	8 weeks	17.6	6.1	15.5-19.7	24.6	7.3	22.1-27.1	<0.001
	6 months	28.8	6.1	26.7-30.9	27.1	5.6	25.2-29.0	0.229
	12 months	31.6	6.2	29.5-33.7	30.5	5.6	28.5-32.4	0.421
Sport/Rec	Pre OP	15.9	8.6	12.9-18.8	15.9	9.2	12.7-19.0	0.967
	8 weeks	-0.1	11.6	(-4.1)-3.8	7.1	11.5	3.1-11.0	0.011
	6 months	7.6	10.7	3.9-11.2	6.7	12.1	2.6-10.9	0.754
	12 months	7.3	10.1	3.8-10.8	7.4	10.7	3.7-11.1	0.954
QOL	Pre OP	23.2	5.2	21.4-25.0	24.8	4.9	23.1-26.5	0.246
	8 weeks	41.4	9.2	38.2-44.6	56.3	9.0	53.2-59.3	<0.001
	6 months	58.1	8.0	55.3-60.8	56.2	9.4	53.0-59.5	0.382
	12 months	60.7	8.5	57.8-63.6	59.2	9.4	56.0-62.4	0.485

Table 3. Absolute changes for all subscales from baseline (preoperative) until 12 months are presented.

Knee range of motion: At discharge, 90% of all patients had obtained full extension, and at 6-month follow-up, all patients had full extension. Flexion was measured preoperatively and during a 12-month follow-up period (Fig. 9). There was no significant difference in preoperative ROM between the two groups (non-Tq 107.9 ± 9.6 degrees) vs. Tq group 107.4 ± 10.5 degrees; p = 0.836). Postoperatively there was significantly better knee ROM in the non-Tq group (47.5 ± 9.5 degrees vs. 35.6 ± 7.9 degrees; p < 0.001). This finding was still detectable at 8 weeks, at which time the non-Tq group had significantly better knee ROM (99.8 ±7.2 degrees vs. 93.4 ± 8.2 degrees; p = 0.002). At 6 months, there was no difference between the non-Tq group and the Tq group: (108 ± 8.5 degrees vs. 107.1 ± 10.6 degrees; p = 0.726).

This was also registered at 1- year evaluation, where no difference was found between the two groups (113.4 ± 8 degrees vs.113 ± 8 degrees; p=0.845).

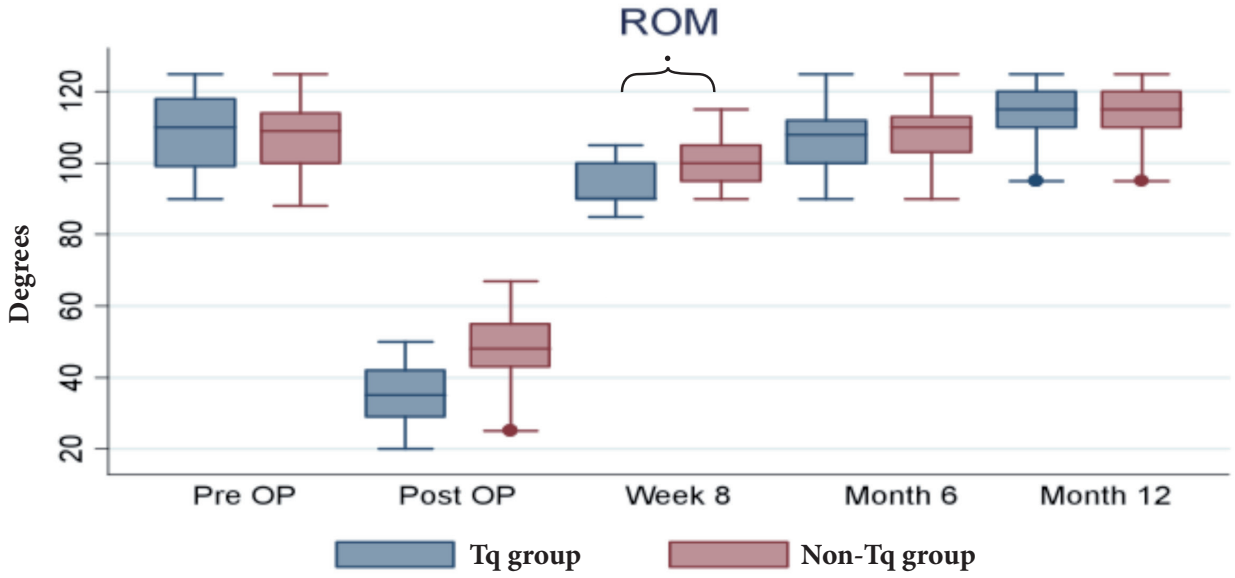


Fig. 9. Range of motion. A significant better ROM was achieved postoperatively and at 8 week follow-up when a tourniquet was not used.

Secondary outcomes:

Pain: A significantly lower mean VAS score on day of discharge was registered in the non-Tq group (4.6 ± 1.4 vs. 5.5 ±1.6; p < 0.015) (Fig. 10).

No difference was registered on postoperative day 0 and again at 8-week follow-up. Patients in the tourniquet group had a greater analgesic consumption and greater discomfort from the thigh until 2 to 3 weeks after discharge. In the Tq group, significantly higher equianalgesic morphine use was registered during hospitalization: 38 ± 9.8 mg vs. 31± 6.1 mg.

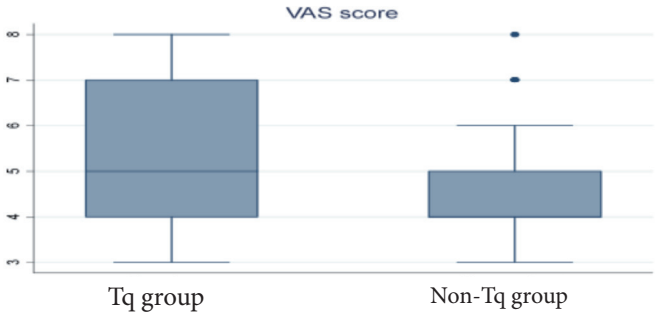


Fig. 10. Mean of all consecutive pain measurements during first 3 days.

Intraoperative bleeding: was significant greater when a tourniquet was not used (Table 4). None of the patients required transfusion during hospitalization.

Surgical time: There was no significant difference between the two groups regarding surgical time in the Tq group (69.5 ± 5.3) compared to the non-Tq group (71.3 ± 4.5 minutes; p = 0.16).

No significant differences were found in surgical visibility (p = 0.12). Obtaining a dry and well-exposed tibia surface for cementing was no challenge – especially after high pulse lavage and swab packing.

Adverse events: Deep vein thrombosis (DVT) was suspected and confirmed by ultrasonography in both groups: 1 in non-Tq group and 2 in Tq group.

At week 8, two patients from the Tq group had flexion <90^0 that required forced manipulation in general anesthesia.

During hospitalization and the postoperative period there was not no excessive oozing of blood or wound complications. This was confirmed during outpatient control.

	Tourniquet			No tourniquet			
	mean	SD	95% CI	mean	SD	95% CI	p- value
Surgical time (min)	69.5	5.3	67.5-71.4	71.3	4.5	69.6-72.9	0.160
Blood loss (mL)	140.3	32.7	128.3-152.3	279.8	52	261.4-298.3	<0.001
Visibility	1.2	0.4	1.0-1.3	1.5	0.7	1.2-1.7	0.120

Table 4. Intraoperative measurements

STUDY II

Hypothesis

Tourniquet use induces ischemia during TKA surgery and reperfusion.

The duration of ischemia was 74.4 ± 3.7 minutes in the tourniquet group. Using microdialysis, changes measured during surgery and reperfusion are expressed in percentages of baseline values (Figure) and in absolute values (Table)

Before surgery, MiD catheters were inserted, and the average of the first consecutive samples before performing surgery were used to establish a baseline and defined as 100% for me tabolites. Baseline was measured after an initial 40-minute flushing period followed by a stabilization period of 20 minutes (table 5).

In the reference leg, baseline reached stable values within that period of time, stable values were reached during baseline and remained unchanged for the whole period of 300 min.

Glucose (mmol/L)	5.0 ± 2.0
Pyruvate (µmol/L)	64.9 ± 10.4
Lactate (mmol/L)	1.8 ±0.4
Glycerol (µmol/L)	84.5 +/12.6
L/P ratio	28.3±3

Table 5. Average interstitial baseline concentration at a constant flow rate of 0.3 µl/min.

Comparison between Tq group and non-Tq group.

Comparing the Tq group with non-Tq group, differences were registered in all of the metabolites from beginning of the reperfusion time until 140–180 min later. After that, there were no difference, and the metabolites were restored back to initial levels.

This is expressed in Figure 11 where the mean differences between the two groups are shown.

Tourniquet group

After a period of tourniquet-induced ischemia, the concentration of glucose decreased by 54% (2.3 ± 0.7 mmol/L; $p < 0.001$), this reduction was detectable during reperfusion, and glucose levels were normalized to baseline 300 min postoperatively.

Pyruvate concentration was initially reduced to 60% (25.9 ± 5.6 µmol/L; $p < 0.001$), while it was dramatically elevated during the first period of 30–60 min of reperfusion to 123% (145.6 ± 10.9 µmol/L; $p < 0.001$). At 180 min, pyruvate concentration was back at baseline, and no difference was detected ($p = 0.118$).

Concentration of lactate increased significantly during reperfusion of 30–60 min up to 116% (3.9 ± 0.8 mmol/L; $p < 0.001$). After 120 min of reperfusion, it slowly returned to baseline ($p = 0.129$). After 300 min, no significant difference was registered ($p = 0.952$) when comparing to baseline (Fig. 12).

Concentration of glycerol also increased dramatically at the beginning of reperfusion to 190% (244.7 ± 12.5 µmol/L; $p < 0.001$) and stayed significantly increased during 140 min of reperfusion ($p < 0.001$). At 300 min, there was no significant difference ($p = 0.634$).

L/P ratio increased significantly 79% (107 ± 33.3) after period of ischemia, but after 90 minutes of reperfusion the initial level was restored.

Significant differences in all metabolites were noted until 140 min. between the operated leg and non-operated leg (Fig 13). All values returned to baseline values within 300 minutes in both legs, after which no difference was registered.

Non-tourniquet group (non ischemic control group):

The metabolites were less affected and returned faster back to initial levels (Fig 14).

The first sample after surgery showed a glucose concentration that only decreased 11.5% (4.6 ± 0.7 mmol/L; $p < 0.001$) during surgery, and during 90 minutes of reperfusion, normal levels were reached ($p = 0.220$).

Pyruvate concentration was reduced to 13.5% (53.8 ± 9.5 µmol/L) of the initial value, and during a short reperfusion period of 30 minutes, it was back to baseline.

Concentration of lactate increased during early reperfusion, and at 30 minutes it reached a maximum of 30% (2.6 ± 0.5 mmol/L). After 60 minutes, it was unaltered, and no statistically significant difference was registered.

Glycerol concentration was increased to maximum of 48% (114.5 ± 15.4. µmol/L) 60 minutes postoperatively. During a long postoperative period, it slowly returned to normal (Fig 14).

L/P ratio also changed significantly, reaching a maximum at 30 minutes reperfusion, 45% (42.2 ± 13.3; $p < 0.001$), but after this, it was quickly restored. The differences between operated and non-operated leg did not indicate an effect due to ischemia, but rather to cell damage as a response to surgery, which was expressed as an increase in glycerol (Fig.15)

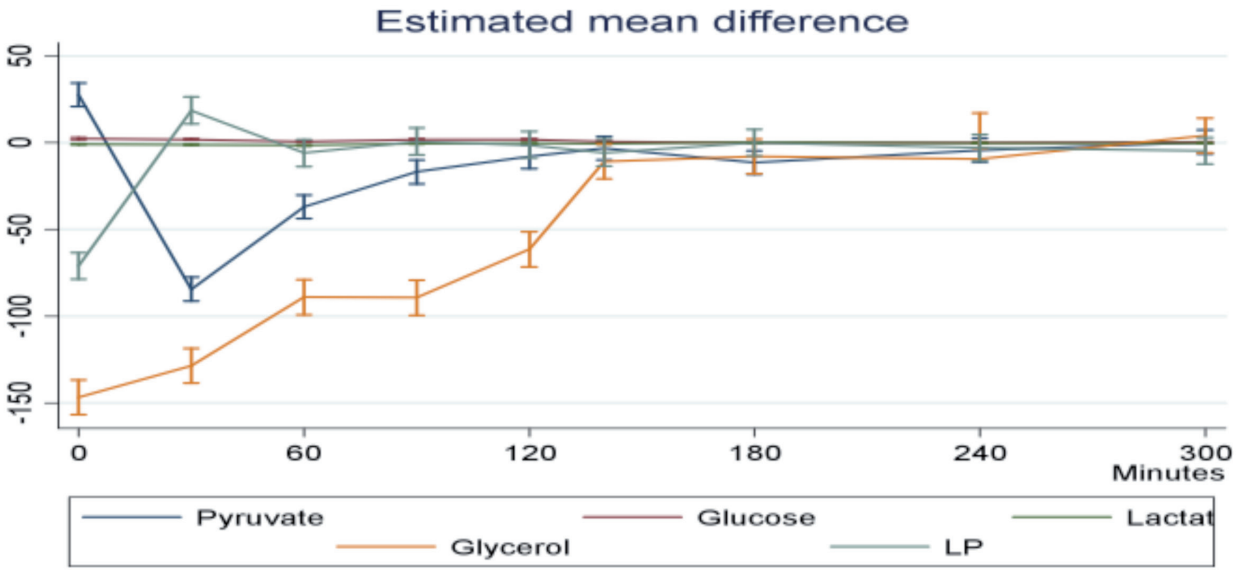


Fig. 11. Tourniquet use induced significant ischemia, and differences in the levels of all the metabolites were detected between the Tq group and the non-Tq group from the beginning of the reperfusion time and until 140–180 min later.

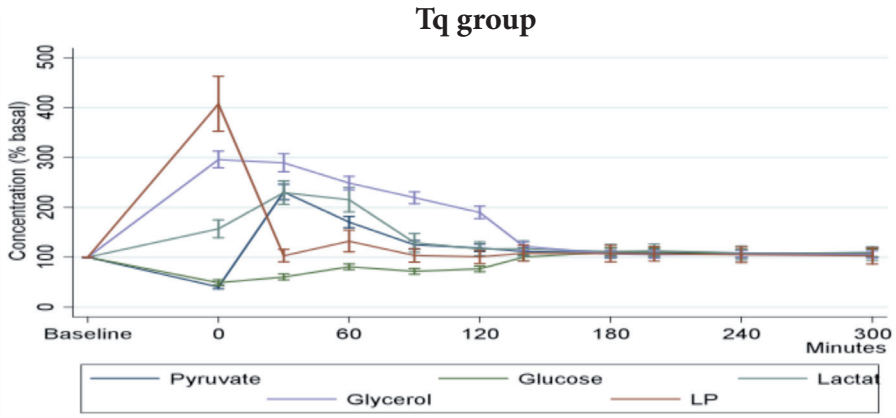


Fig. 12. Absolute values in percentile change from baseline. The ischemic changes are restored after a 300 minutes.

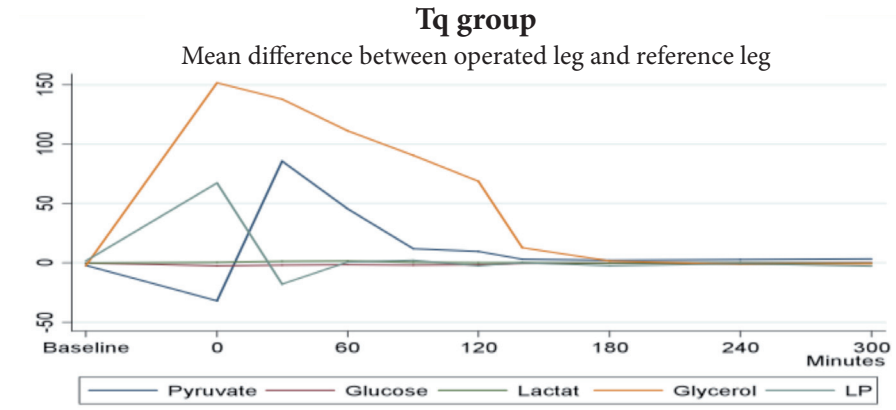


Fig. 13. Mean difference between operated leg and reference leg in the TQ group. Significant differences in metabolites were noted until 140 min.

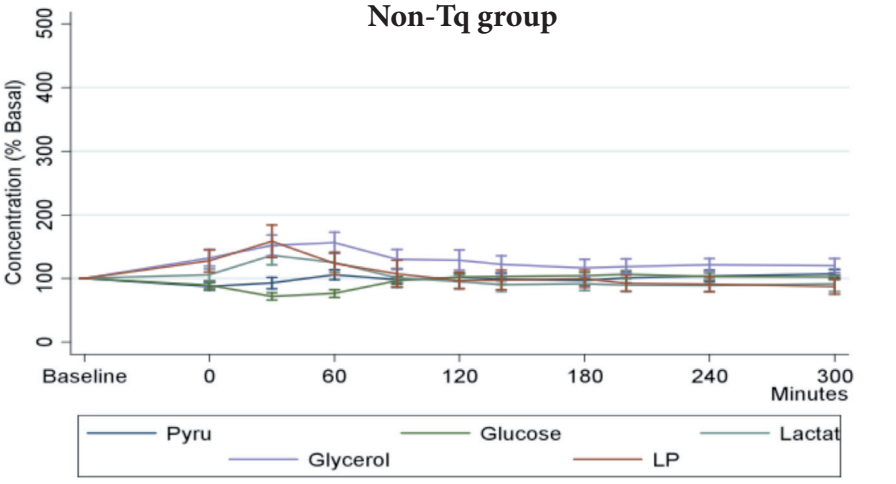


Fig. 14. In non-Tq group metabolite changes were smaller and restored within 60 min.

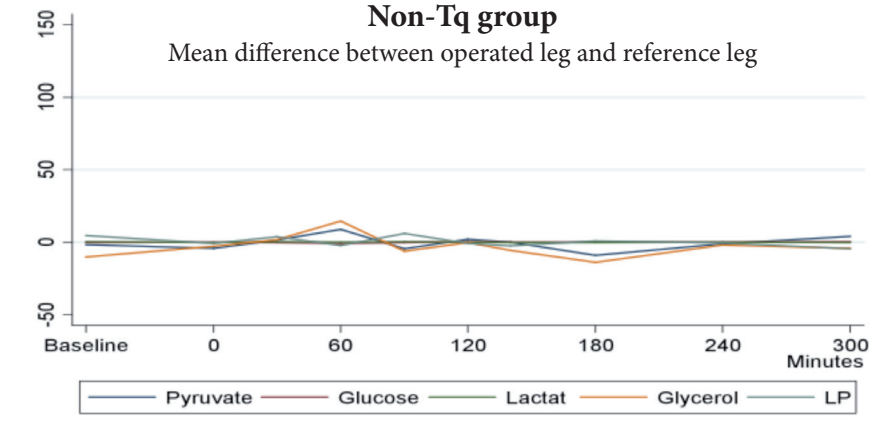


Fig. 15. Mean difference in non Tq-group between operated leg and reference leg. Glycerol is affected due to cell damage as a response to surgery. Ischemic metabolites are not affected.

Study III

Hypothesis

Absence of a tourniquet does not negatively affect the quality of cement-tibial fixation.

During 2 years' follow-up, no statistically significant difference was detected in the mean values of MTPM between the two groups (p = 0.63) (Fig.16). No statistically significant difference was detected in mean values of translations or rotations along the sagittal, transverse and longitudinal axes at any time during follow-up and after 2 years, p>0.05. The mean were all below 0.5 mm and 0.5 degrees for both groups (table 6).

In both groups, all of the patients analyzed with RSA showed stable fixation throughout the follow-ups, and no significant migration was detected.

Adverse event: We registered one case of early tibial component loosening in the Tq group. The patient was initially without symptoms and well mobilized, but on plain radiographs the loosening was detected at week 8. Implant loosening had occurred due to impaired subchondral tibia bone quality caused by a cyst not recognized before or during surgery. This patient was not included in the RSA study.

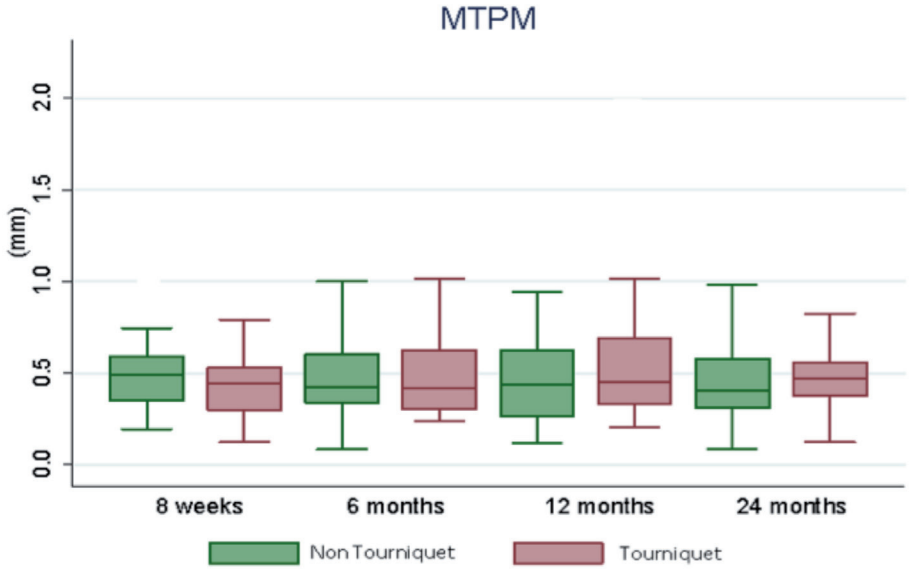


Fig. 16. MTPM Maximum total point motion during a 2-year follow-up. No difference was found between the two groups.

	8 weeks		6 months		12 months		24 months	
N = 57	Tq n=29	Non-Tq n=28	Tq n=29	Non-Tq n=28	Tq n=29	Non-Tq n=28	Tq n=29	Non-Tq n=28
X translation (mm±SD)	0.07±0.39	0.01±0.14	0.02±0.33	-0.01±0.22	0.04±0.30	-0.03±.030	0.03±0.28	-0.04±.31
Y translation (mm±SD)	-0.02±0.15	-0.01±0.11	-0.04±0.15	-0.02±0.13	0.02±0.23	-0.01±0.11	-0.03±0.18	-0.02±0.27
Z translation (mm±SD)	-0.01±0.17	0.04±0.20	0.05±0.12	0.03±0.32	-0.03±0.50	0.01±0.35	-0.02±0.22	0.02±0.28
X rotation (degrees±SD)	-0.09±0.41	0.01±0.34	0.02±0.35	-0.04±0.50	-0.02±0.57	-0.13±0.50	-0.03±0.47	-0.03±0.31
Y rotation (degrees±SD)	-0.08±0.98	0.07±0.75	-0.05±0.95	0.11±0.83	-0.09±0.96	-0.30±0.81	-0.12±0.88	-0.08±0.93
Z rotation (degrees±SD)	-0.16±0.45	-0,04±0.34	0.07±0.30	0.03±0.62	0.02±0.28	-0.10±0.54	0.04±0.41	-0.05±0.58
MTPM mean (mm±SD)	0.43±0.22	0.53±0.32	0.55±0.42	0.51±0.34	0.57±0.40	0.53±0.43	0.47±0.16	0.45±0.21

Table 6. RSA results expressed as mean translation and rotation of the tibial component. Positive directions for translation along orthogonal axis were X (medial-lateral), Y (caudal-cranial), Z (posterior-anterior). Positive directions for rotation around the coordinate axes were X (anterior posterior tilt), Y (internal-external rotation), Z (varus-valgus tilt).

Discussion

The clinical outcomes, pain reduction and a good knee range of motion, are important endpoints that determine the success of TKA surgery. Another success criterion is long-term durability, achieved by obtaining a good quality of cementation so that implant fixation is assured.
The aim of the thesis was to investigate the effect of tourniquet use during TKA on clinical outcomes regarding rehabilitation and knee range of motion. Intraoperative measurements, i.e. surgical visibility, operation time and blood loss were also registered. Furthermore, the ischemic changes during and after surgery and implant fixation was evaluated, since these subjects have only been investigated to a limited extent. The overall aim was to optimize the TKA procedure so that no unnecessary procedures were used which might delay rehabilitation. The early period of rehabilitation is crucial. Patients that are mobile and can commence rehabilitation quicker have increased chances of better clinical and functional results.

Study I showed significantly better clinical and functional outcome in terms of better KOOS scores and easier mobilization with better knee ROM in the initial rehabilitation stage when a tourniquet was not used. Pain during TKA is inevitable because of the surgical trauma to soft tissues and osseous structures. Patients undergoing surgery in which a tourniquet was used often complained of thigh pain at the site of the tourniquet. It is possible that local pressure on nerves and soft tissue is the cause, and this has been revealed in previous studies [63, 64].
The increased pain was confirmed by the KOOS registration. All patients in the non-Tq group had significantly better scores until the 6-month outpatient control, after which no significant differences were detectable. Not using a tourniquet facilitated easier rehabilitation without patients experiencing additional pain from the thigh.

We found that knee ROM recovery was achieved faster in the non-Tq group than in the Tq group, which was also noted by Wakankar et al. (1999) and Chang et al. (2012) [59, 65]. We found that early postoperative benefits were better knee ROM and better subjective knee performance observed at the outpatient follow-ups until 6 months after surgery. However, the clinical differences between the groups did decrease with time. These findings are in accordance with Ledin et al. (2012) [7], who found pain was increased during the first 4 postoperative days and knee ROM was still decreased at 2 years when a tourniquet was used. Vandenbussche et al. (2002) and Li et al. (2009) also found early improvement in knee flexion and reduction of initial postoperative pain [38, 66]. Increased pain and thigh swelling could be attributed to the tourniquet, and these conditions could impair initial knee flexion and thereby rehabilitation.
Tai et al. (2012) found decreased postoperative pain when a tourniquet was not used, but no difference in knee flexion. This did not affect the rehabilitation progress or recovery [18].

We found no differences in surgical time or intraoperative visibility and controlling bleeding was not a problem. Pre- and postoperative tranexamic acid was given, and during initial surgery, the knee was flexed so that further hemostasis was achieved. Surgical time is an interesting parameter since it represents an objective measure of difficulties caused by impaired visibility. Since there was no difference in surgical time, it appears that not using a tourniquet had no effect on surgical visibility.
Smith et al. (2010) and Zhang et al. (2010) found that intraoperative bleeding is reduced with tourniquet application but that tourniquet application had no benefits with regard to postoperative bleeding, total blood loss or transfusion rates [5, 67]. We found less intraoperative bleeding with tourniquet use; this however did not have any clinical relevance. Perioperative blood loss was assessed on the basis of maximum hemoglobin reduction – a common evaluation in clinical practice. Hemoglobin was monitored in all patients during hospitalization and not a single patient required transfusion. Tetro et al. (2001)suggested that using a tourniquet was not effective in reducing overall blood loss volume; a conclusion also reached in meta-analyses by Smith et al. (2010) and Tai et al. (2011) [5, 25, 28].

In study II, we revealed that microdialysis was an effective way to monitor interstitial levels of different metabolites associated with ischemia in skeletal muscle. The apparent ischemia underneath the tourniquet has previously been described [21, 81]. We estimated metabolic changes distally in the limb exposed to tourniquet-induced ischemia and during reperfusion. The main findings showed that tourniquet use inflicts significant ischemia in the affected limb and these changes last until 3 hours after cuff deflation.
The difference between the two groups, as illustrated in Fig.10, shows the differences tourniquet use induces in the metabolic markers, which are affected until 180 minutes after tourniquet release. If the systemic effect of surgery on the markers is ruled out, it can be concluded that difference was due to the local effect of the tourniquet.
In the non-tourniquet group, the markers changed right after surgery compared to baseline in the operated leg, but not to the same extent as in the tourniquet group, and they quickly reverted back to normal values.

Comparing the operated leg and reference leg, there was no significant difference, indicating that here a local response did not occur and that the changes were due to an overall systemic response to surgery.

Study III assessed one of the main reasons for tourniquet application. This concerns the question of whether better implant fixation is achieved with the use of a tourniquet. It is known that tibial components migrate after surgery, most markedly in the first 6 weeks; later, migration diminishes and stabilizes approximately 1 year after surgery [35, 69, 70]. Obtaining a good and secure initial fixation is of utmost importance.
Using RSA and MTPM as primary outcome we did not register any difference in terms of implant migration during the first 2 years after surgery. Furthermore, no difference in the translation and rotations between the two groups was detected.
To our knowledge this is the first study to investigate the effect of a tourniquet on implant migration and long-term survival using model-based RSA. Only two other studies regarding implant fixation and tourniquet have been conducted; both used marker-based RSA and involved 50 patients and 60 patients, respectively [7, 8]. Their results support our findings. MTPM and translations and rotations after 2 years showed no difference
In the randomized study by Vandenbussche et al. in (2002), plain radiograph analysis was performed at 3 months, looking for early signs of aseptic implant loosening, with special attention to radiolucent lines, and no difference was seen in relation to tourniquet use or non-use [38]. Abdel-Salam and Eyres (1995) also reported that no difference was detected between the two groups based on an evaluation of plain radiographs during a 2-year follow-up [1].
MTPM between the two groups showed no difference in migration or rigid body motion pattern, indicating that the absence of a tourniquet did not impair the fixation of the tibial component and thereby did not increase the risk of long-term loosening.

Results in a clinical context

The results from all three studies seem to support the notion that not using a tourniquet does not impair the outcome of TKA surgery. In fact, in studies I and II, the outcomes were favorable when not applying a tourniquet, and study III revealed no advantage in obtaining a better tibial implant fixation with tourniquet application.
If not using a tourniquet can facilitate an earlier achievement of functional outcomes after TKA and less postoperative pain, consequently the future use of a tourniquet should be reconsidered in order to avoid complications associated with its use.
The results of this study is limited by the fact all patients were operated by the same experienced surgeon and patients are carefully included if eligible for this study. It should be taken into consideration that TKA surgery without tourniquet may not be suitable for low-volume surgeons.

Conclusion

The studies included in the present thesis investigated the value of a tourniquet in cemented TKA surgery, with regard to clinical outcomes, ischemic conditions and implant fixation. In all three studies, we found no benefit of tourniquet application. The use of a tourniquet should be kept to a minimum and serve as a backup technique if excessive bleeding occurs. Implant fixation is of utmost importance and has previously been investigated in two other RSA studies. Together with present RSA study, the indication is that absence of a tourniquet in cemented TKA does not impair fixation. Reporting to national registers should be done to support the findings of the studies in this thesis.

Suggestions for future research

Our results have shown that the clinical practice could be altered so that a tourniquet is not used as a standard procedure in cemented TKA. There are many aspects that should carefully be taken account of when using the tourniquet. The direct mechanical compression can cause nerve palsy, and therefore investigating the extent of nerve damage could be interesting.
The cementation technique is an area that has not been investigated in this study. Whether a conventional one-stage versus a two-stage cementation procedure is optimal and whether the use of anchorage holes should be performed could be studied. Therefore further randomized trials are suggested to clarify these aspects.

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Appendix: Studies in full text

Paper:

I. The Value of Tourniquet Application in Total Knee Arthroplasty: A Randomized Study of 70 Patients.
Ashir Ejaz, Anders C. Laursen, Andreas Kappel, Mogens B. Laursen, Thomas Jakobsen, Sten Rasmussen, Poul Torben Nielsen.
(Accepted in Acta Orthopaedica 2014)

II. Tourniquet Induced Ischemia and Changes in Metabolism during TKA: A Randomized Study Using Microdialysis.
Ashir Ejaz, Anders C. Laursen , Andreas Kappel, Thomas Jakobsen, Poul Torben Nielsen, Sten Rasmussen.
(Submitted)

III. Absence of a tourniquet does not affect fixation of cemented TKA: a randomized RSA study of 70 patients.
Ashir Ejaz, Anders C. Laursen, Andreas Kappel, Thomas Jakobsen, Sten Rasmussen, Poul Torben Nielsen, Mogens B. Laursen.
(Submitted)