UNIVERSITÄT
BERN

MASTER THESIS

Awarding the academic title of

Master of Medicine (M Med)

Medical Faculty, University of Bern

Postoperative Pain in Tourniquet Induced Ischemia-Reperfusion Injury in Total Knee Arthroplasty

A randomized single-blinded case-control clinical pilot trial

Master Thesis submitted by

Jelena Sarah Kummer

Immatriculation Nr. (15934110)

Handed in on the14th of May 2020

For the degree of

Master of Medicine (M Med)

Supervisor: Prof. Dr. phil. nat. Robert Rieben

Department for BioMedical Research, Bern

Medical Faculty of the University of Bern

Co-Advisors: PD Dr. med. Frank Klenke and Dr. med. Emanuel Liechti

Department of Orthopedic Surgery Inselspital Bern

Dr. Mai Abd El Hafez and Jane Shaw Boden

Department for BioMedical Research, Bern

Contents

1 Abstract

Total knee arthroplasty (TKA) is an elective and effective surgical procedure to overcome chronic pain and mobility limitation due to osteoarthritis and improves life quality.[1] During TKA the aim of the tourniquet, an inflatable cuff, is to provide a bloodless surgical field and therefore facilitate cementation.[2,3] The tourniquet induces ischemia and leads to ischemia-reperfusion injury (I/R injury).[4]

The aim of the randomized, single-blinded case-control clinical pilot trial is to investigate postoperative pain after long-term ischemia due to the use of a tourniquet in TKA. Postoperative pain in 48 p.op. hours was assessed by comparing the total opioid consumption, mean numeric rating scale (NRS), the highest rated intervention according to the WHO analgesic ladder as well as numbers of patients who required patient controlled intravenous analgesia (PCIA). In this first interim analysis, the first twenty patients of which ten either underwent short (mean = 30.1 min, SD = 4.7, range = 21-41) or long ischemia (mean = 111.4 min SD = 14.0, range = 90-127) were compared. The long ischemia group showed a significantly higher intervention in analgesic treatment according to the WHO analgesic ladder (3.6 vs. 2.8, $p = 0.04$). Patients in the long ischemia group also required significantly more PCIA (6 vs. 0 $p < 0.01$). There was also a trend towards more total opioid consumption (79.5 vs. 113.9 mg p.o. morphine). There was no difference in the mean of NRS between the short and long ischemia group. Further twenty respectively forty patients might substantiate these findings.

2 Background

2.1 Pathophysiology of ischemia-reperfusion injury

I/R injury is a complex local but also systemic inflammatory reaction of a previously ischemic tissue.[5] It is known that reperfusion of an organ or a tissue that has been ischemic for a prolonged period of time can lead to I/R injury.[6] I/R injury has been intensively investigated in past decades as it plays a role in many different standard medical and surgical procedures such as organ transplantations, cardiopulmonary bypass and many more.[6]

When ischemia occurs in a tissue it is accompanied by a change in the energy supply and cellular changes.[6] During ischemia, reactive oxygen species are produced as well as cytokines and so called 'danger signals' are expressed on cell surfaces.[7,8] Reperfusion then leads to a sterile inflammation by activation of the innate immune system, natural antibody recognition of the neoantigens, endothelial activation as well as activation of the complement system.[8,9] The complement system is a cascade, consisting of more than thirty proteins, acting as enzymes activating other proteins in the cascade.[10] Weiser et al have shown that the complement system and natural antibody recognition mediate I/R injury.[11] Activation of complement system has been shown to be an early event in I/R injury that is why inhibiting its activation or its components may protect tissue after reperfusion.[8] In rat hind limb models I/R injury was prevented by giving C1-inhibitor before application of the tourniquet.[12] Other studies have shown that mice deficient in immunoglobulins or C3 and C4 have less I/R injury.[8]

2.2 Tourniquet in total knee arthroplasty

Total Knee Arthroplasty (TKA) is an elective and effective surgical procedure to overcome chronic pain and mobility limitation due to osteoarthritis and improves life quality.[1] During TKA, a tourniquet, an inflatable cuff, is used to provide a bloodless surgical field and therefore facilitate cementation.[2,3] The time of ischemia depends nowadays mostly on the surgical procedure and the surgeons' preference as no clear guidelines have been established.[2]

After TKA patients face edema and postoperative pain in the lower limb. This is often thought to be an effect of surgical trauma but the use of a tourniquet is controversial as studies linked it to more edema formation in the lower limb[13], postoperative pain[13,14] and therefore higher opioid consumption[5].

A feared complication is the post-tourniquet syndrome (stiffness, pain, weakness and subjective numbness) which is known to be a result of different pathogenic mechanisms including muscle ischemia.[5] I/R injury in the context of tourniquet use in TKA has not been investigated in detail but is known to lead to muscle damage as skeletal muscle is thought to be the tissue most vulnerable to ischemia in the lower limb.[15] In a mouse model study, I/R injury also lead to more sensitization of the afferent neurons.[13]

2.3 Postoperative pain

Pain is according to the International Association for the Study of Pain, "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*."[16,17] Pain is a complex phenomenon influenced by many different factors. In the pathophysiology of postoperative pain not only local but also central sensitization are involved.[18] Here the main focus will be on local factors. Apart from direct nerve injury due to surgical trauma the lower pH and the decreased oxygen tension are associated with peripheral sensitization.[19] But there are also acid-sensing ion channels that can directly transduce this ischemic-like signal.[19] Apart from activation of immune system, along with the release of cytokines, activation of immune cells is also known to influence peripheral sensitization.[19]

2.4 Analgesic groups

There are different groups of analgesics because there are different points in the pain pathway where a substance can operate. These targets might be peripheral as well as central.[20] The main analgesic groups are described below.

2.4.1 Non-opioid analgesics

Non-opioid analgesics have only low analgesic potency compared to opioids. However, they might reduce opioid consumption and therefore have an opioid sparing effect.[21]

NSAID stands for non-steroidal-anti-inflammatory-drugs.[22] These are analgesics as well as anti-inflammatory drugs and act by inhibiting the cyclooxygenase (COX) in the tissue.[17] COX is an enzyme acting on the production of thromboxanes and prostaglandins.[17] Thromboxanes and prostaglandins mediate local pain as well as playing a major role in inflammatory response and fever.[22] There are two different types: COX-1 and COX-2.[22] NSAID differ in affinity and reversibility of inhibiting those enzymes.[22] Main side-effect is gastrointestinal bleeding.[17]

Compared to NSAID metamizole and paracetamol have no gastrointestinal side-effects. **Metamizole** is a pyrazole derivative[22]. Apart from strong analgesic, antipyretic and anti-inflammatory effect, there is also a spasmolytic effect.[22] **Paracetamol** is an aniline derivative.[22] It is often used for mild to moderate pain and has no anti-inflammatory effect.[23]

2.4.2 Opioids

Opioids have a very strong analgesic but no anti-inflammatory and antipyretic effect.[22] They are acting on the central nervous system.[22] The major effect of opioids is mediated by interaction with μ-receptors.[22] There are different derivates of morphine which have greater or lesser analgesic potential.[22]

2.4.3 Patient controlled intravenous analgesia

Patient Controlled Intravenous Analgesia (PCIA) is an established and appreciated postoperative therapy.[17] It is an analgesic method used when patients experience severe pain.[24] Opioids such as morphine or hydromorphone are used for PCIA.[17] Patients can apply a bolus when they experience pain.[17] Indications for a PCIA are severe postoperative pain, an understanding of PCIA and a recommended minimum age of five years.[17] There are also contraindications such as old age, no understanding of PCIA; hypovolemia, sleep apnoea syndrome, patients with a history of substance abuse, psychiatric diseases, severe obesity.[17]

2.4.4 Co-analgesics

Co-analgesics (also called adjuvants) are substances influencing and intensifying the analgesic effect of a drug.[20] For example, tricyclic antidepressants are known to inhibit pain conduction.[20] Another group of agents with pain-modulating characteristics are neuroleptics such as gabapentin.[20] They are known to intensify the analgesic effect of opioids.[20] Anticonvulsants are also known to modify pain sensation.[20]

2.5 WHO analgesic ladder

Postoperative pain treatment is based on the analgesic ladder the World Health Organization (WHO) established in 1986 primarily for chronic pain in cancer treatment.[21] The ladder proposes non-opioids for mild pain, moving up to stronger opioids for severe pain.[25] The extended version added a fourth step, where PCIA, nerve blocks and other interventional pain treatments are represented (Fig. 1).[25] It is nowadays not only an accepted tool for chronic cancer pain but also for chronic non cancer pain and acute pain.[17] Therefore postoperative pain therapy occurring after TKA also adheres to the WHO analgesic ladder.[17]

Bottom up treatment meaning beginning with low potential analgesics and adding or replacing them by stronger ones is a commonly used approach to postoperative pain.[26] But initial treatment of postoperative pain can also be top down, with an initial relatively high analgesic treatment that can be stepped down if tolerated.[25] Both approaches are meant to respond adequately to a patients subjective experience of pain.[17,25]

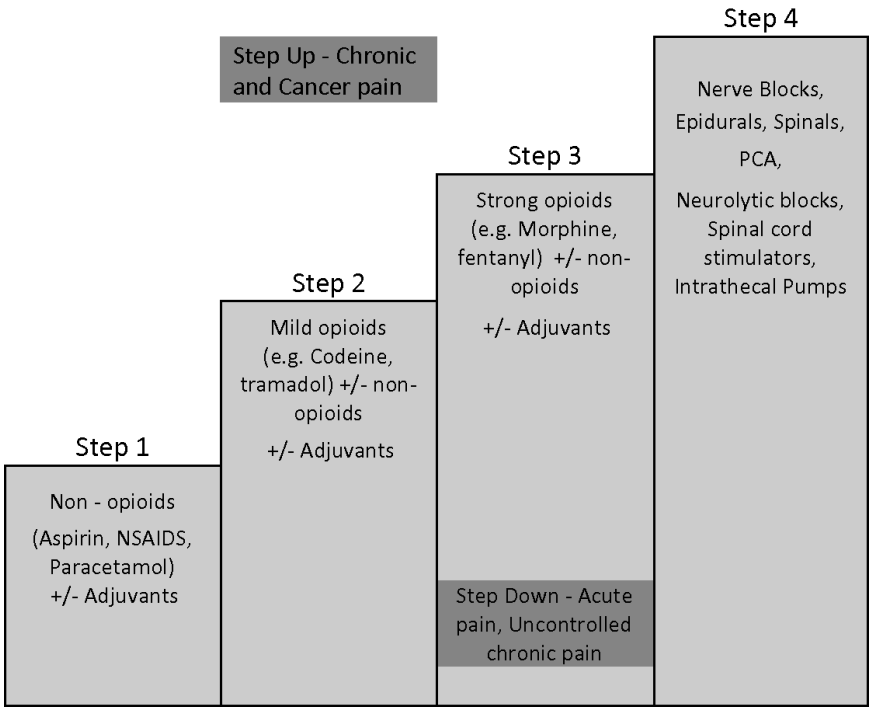

Fig. 1 Adapted analgesic ladder for acute, chronic and cancer pain.[25]

Step one consists of non-opioid analgesics that progresses to step two, which includes low potential opioids in combination with non-opioids. The third step is for severe pain where strong opioids are used. The fourth step represents invasive treatment such as PCIA.

3 Aim of the study

The aim of this randomized, single-blinded case-control clinical pilot trial is to investigate postoperative pain, associated with tourniquet induced I/R injury after different times of ischemia (more than 90 min vs. 30 min). A total of 60 patients undertaking TKA will be randomized in two groups, undergoing either short or long ischemia. Both modalities are standard clinical practice. At our centre, the choice for short or long application is currently made by the surgeon and clear guidelines are missing. The study is also meant to provide basis for such guidelines and intended to power for future interventional studies in which for example inhibitors of the plasma cascade systems like C1-inhibitor could be used.

The hypothesis of this study was that prolonged tourniquet time in TKA results in more I/R injury. The purpose of this fist interim analysis is to narrow the set of analyses for the second interim and main analysis.

This master thesis investigates postoperative pain in the first twenty of the planned sixty patients, which were randomized into two groups of ten, one with short ischemia and the other with long ischemia. The aim was to determine differences between short and long ischemia regarding total opioid consumption, mean of numeric rating scale (NRS), the highest rated intervention according to the WHO analgesic ladder and number of patients who required patient controlled intravenous analgesia (PCIA) in 48 postoperative hours. Pro-inflammatory markers and cytokines will not be considered in this master thesis.

4 Methodology

A randomized, single-blinded case-control clinical pilot trial was chosen as the study design. The study protocol was approved by the Competent Ethics Committee (registration number ISRCTN87180032).

4.1 Patient selection

A total of twenty patients, separated in two groups of ten, aged between 18 – 90 years undergoing TKA with the use of a tourniquet in a single institution were included in the study. Every patient needed to sign an informed consent before being included. Patients were included in the study for 48 hours after surgical wound closure. After 48 hours some patients may already leave hospital therefore further follow-up was not planned.
Randomisation of the two groups was done electronically, and sealed envelopes were handed to the surgeon, so one group underwent ischemia only occurring during the cementation of the knee prosthesis (around 30 min), the other group during the whole operation time (more than 90 min).
The C-reactive protein value, an indicator for systemic inflammation, was required to be less than 10mg/l twelve hours before surgery started. Exclusion criteria were pregnancy or breast feeding. Steroids and other drugs affecting the innate or adaptive immune system were also an exclusion criterion, as well as history of thromboembolic events.

4.2 Intervention

Patients undergoing a TKA under general or spinal anaesthesia underwent either short or long ischemia. Both interventions are accepted surgical procedures and depend on the surgeon's preference as no clear guidelines have been evolved so far. Surgeons estimate the tourniquet pressure based on the patients' intraoperative systolic blood pressure prior to tourniquet inflation. Systolic blood pressure is documented in the anaesthetic chart.

4.2.1 Experimental intervention – long ischemia

Application of a standard tourniquet (Automatic Tourniquet System ATS 4000, Zimmer, USA) for the entire duration of surgery (90 – 120 min). The tourniquet was placed 20 cm above the knee and inflated 10–20 min after induction of general anaesthesia after skin incision as this is the case in common clinical practice. The tourniquet was deflated after wound closure.

4.2.2 Control intervention – short ischemia

Application of a standard tourniquet (Automatic Tourniquet System ATS 4000, Zimmer, USA) for around 30 min. The tourniquet was placed 20 cm above the knee and inflated just before cementing of the knee prosthesis. The tourniquet was deflated immediately after the cementation process was completed.

4.3 Post-randomization exclusion

Patients who were randomised and did not receive an intervention were excluded as this was the case for one patient in the long intervention group. This is a legitimate post-randomisation criterion.[27] The patient was replaced by another patient previously randomly assigned to the long intervention group.

4.4 Data collection

Data collection was performed with the digital medicine registration system i-pdos. Information on exposure of tourniquet time, tourniquet pressure, anaesthesia, systolic blood pressure prior to tourniquet inflation and installation of a PCIA was found in the anaesthetic chart. Pre- and postoperative consumption of opioids, postoperative consumption of non-opioid analgesics (paracetamol, metamizole, ibuprofen) as well as any demographic and anamnestic data was documented in the patients file.

4.5 Secondary outcome - total opioid consumption

Secondary outcome is total opioid consumption during the first 48 postoperative (p. op.) hours. Extracting data on the doses of all opioids administered to the patient was performed. This dose was converted into equipotent doses of per os morphine in milligrams. The converting factor from oral oxycodone to oral morphine was 1.5 and from intravenous hydromorphone to oral morphine 11.[28]

There is documentation of what medicine had been prescribed for the patient, and what medicines were actually given to the patient by nurses. We extracted data on the documented medicine nurses had given to the patient.

4.6 Tertiary outcomes

Tertiary outcomes for postoperative pain are mean of NRS, analgesic intervention according to four-step WHO analgesic ladder and number of patients who used PCIA in the first 48 p.op. hours

NRS is a tool to measure pain in adults. The most common NRS is with 11 items from 0 up to 10.[29] Both extremes are anchored with terms: 0 stands for «no pain» whereas 10 means «worst pain imaginable».[29] NRS was obtained by nurses when the patient returned to the

ward up to 48 p.op. hours. Documented scores for each patient performed in the 48 p.op. hours were between one and ten.
The WHO analgesic ladder is a clinical tool to provide sufficient analgesia for patients. Even though it has not been investigated as a tool for evaluating pain in research it might give an impression of the clinical response to patients' pain. The different analgesics each patient has taken were sorted according to the four-step WHO analgesic ladder, which also takes interventional treatment such as PCIA into account. The highest intervention performed up to 48 p.op. hours was considered.
For example, if patient N. 1 got paracetamol, metamizole and oxycodone, the intake was rated with 3 because oxycodone is according to the four-step WHO analgesic ladder a step 3 analgesic.[25] If the patient had a PCIA this was rated with 4. Mean of both groups were compared after 48 p.op. hours.

4.7 Demographic characteristics, pre- and perioperative features

To characterize the cohort and identify possible confounders demographic data, anamnestic, perioperative and postoperative information were analysed.
Analysed demographic factors were age and sex. As anamnestic factors, body mass index (BMI), history of diabetes mellitus, and preoperative consumption of opioids were investigated.
Intraoperative information such as type of anaesthesia, tourniquet time, tourniquet pressure and systolic blood pressure prior to tourniquet inflation were analysed. As a postoperative feature to minimize bias by opioid sparing effect of non-opioid analgesics, the mean intake of metamizole (Novalgin), paracetamol (Dafalgan) and ibuprofen was compared between both groups starting as soon patients got back to their room up to 48 p.op. hours.

4.8 Statistical analysis

Statistical analysis was performed using Graph Pad Prism Version 8.4.0. The secondary outcome was total opioid consumption over 48 p.op. hours. Tertiary outcomes were mean of NRS in 48 p.op. hours, pain treatment according to the four-step WHO analgesic ladder and number of patients using PCIA.
For the intended total of sixty patients a normal distribution can be assumed, therefore, for this first interim analysis of twenty patients, an unpaired t-test was performed for continuous variable. Fisher exact test was used for evaluating categorical variables. A p-value of <0.05 was considered as the level of significance.

5 Results

5.1 Demographic characteristics, pre-and perioperative features

Both groups were similar in terms of age, sex, BMI and incidence of diabetes (Tab. 1). The short ischemia group underwent a mean tourniquet time of 30.1 min (SD = 4.7, range = 21-41). The long ischemia group underwent a mean tourniquet time of 111.4 min (SD = 14.0, range = 90-127). One patient in the long ischemia group experienced 98 min ischemia, 33 min of reperfusion and another 19 min of Ischemia, which was counted as a total of 127min ischemia. The mean tourniquet pressure in the long ischemia group was 322 mmHg (SD = 21.83, range = 270-350) and significantly higher (p = 0.04) than tourniquet pressure in the short ischemia group (299 mmHg, SD = 24.86, range = 300-350) (Tab. 2) Systolic blood pressure was comparable in both groups with a mean of 121 mmHg (SD = 26.9, range = 95-185) in the short vs. 125 mmHg (SD = 21.6, range = 100-160) in the long ischemia group (p = 0.72). No significant difference in anaesthetic procedure was found between both groups. But it has to be mentioned, that in the short ischemia group a patient had to switch from spinal anaesthesia to general anaesthesia for the rest of surgery.

Preoperative intake of opioids were comparable in both groups as well as postoperative consumption of non-opioid analgesics.

Tab. 1 Demographic characteristics

	Short ischemia	Long ischemia	p value
Age in years [a]	66.0 (10.8) 47-81	63.3 (12.2) 44-79	0.61
Sex Female Male	 4 6	 6 4	 0.66
Mean BMI in kg/m^2 [a]	30.3 (4.4) 24.5-37.9	30.6 (6.1)23.6-40.1	0.89
Diabetes mellitus	2	1	>0.99

[a] values: mean (SD) range

Tab. 2 Pre- and perioperative features, postoperative intake of non-opioid analgesics

	Short ischemia	Long ischemia	*p* value
Tourniquet time in min [a]	30.1 (4.7) 21-41	111.4 (14.0) 90-127[x]	<0.01
Tourniquet pressure in mmHg [a]	299 (21.8) 270-350	322 (24.9) 300-350	0.04
Systolic blood pressure prior to tourniquet inflation in mmHg [a]	121 (26.9) 95-185	125 (21.6) 100-160	0.72
Type of anaesthesia General anaesthesia Spinal anaesthesia	 9[y] 1	 9 1	 >0.99
Preoperative opioid consumption p.o morphine in mg [a]	1.5 (4.7) 0.0-15.0	3.8 (11.9) 0.0-37.5	0.58
Postoperative intake of non-opioid analgesics in 48 p.op. h			
Paracetamol in g [a]	4.6 (3.6) 0.0-10.0	2.4 (2.9) 0.0-7.0	0.15
Metamizole in g [a]	5.5 (2.9) 0.0-7.0	5.3 (1.9) 0.0-7.0	0.89
Ibuprofen in g [a]	0.4 (0.8) 0.0-2.0	0.5 (1.1) 0.0-3.0	0.78

[a] values: mean (SD) range
[x] one patient underwent 98 min ischemia, 33 min of reperfusion and another 19 min of ischemia, counted as a total of 127min
[y] one patient first underwent spinal anaesthesia what was changes to general anaesthesia

5.2 Secondary and tertiary outcomes

Total opioid consumption over 48 p.op. hours of the long ischemia group was higher with a mean of 113.9 mg (SD = 115.3, range 7.5-407.7) compared to 79.5 mg in short ischemia group (SD = 61.2 range = 0.0-225.0). The difference was not significant ($p = 0.41$) (Tab. 3 and Fig. 2A).

There was no difference in NRS mean in 48 p.op. hours between short and long ischemia group (3.0 vs. 3.0). Values for each patient documented in the system varied between one to ten during the 48 p.op. hours (Tab. 3 and Fig. 2B).

There was a significantly higher mean of intervention 3.6 (SD = 0.52, range = 3-4) according to the four-step WHO analgesic ladder in the long ischemia group compared to a mean of 2.8 (SD = 0.63, range = 1-3) in the short ischemia group ($p = 0.04$) (Tab. 3 and Fig. 2C). A total of six patients in the long ischemia group required installation of PCIA, whereas in short ischemia group no patients required a PCIA ($p < 0.01$) (Tab. 3 and Fig. 2D). The two groups were comparable in terms of consumption of non-opioid analgesics.

Tab. 3 Secondary and tertiary outcomes

	Short ischemia	Long ischemia	*p* value
Total opioid consumption over 48 p.op h in mg p.o. morphine [a]	79.5 (61.2) 0.0-225.0	113.9 (115.3) 7.5-407.7[x]	0.42
Mean NRS of 48 p.op. h [a]	3.0 (1.8) 0.9-7.0	3.0 (1.4)1.1-5.7	0.95
Intervention according to four-step WHO analgesic ladder in 48 p.op. h [a]	2.8 (0.) 1-3	3.6 (0.5) 3-4	<0.01
Number of patients requiring PCIA in 48h p.op. h	0	6	0.01

[a] values: mean (SD) range
h = hours
p.o. per os
p.op. post-operative

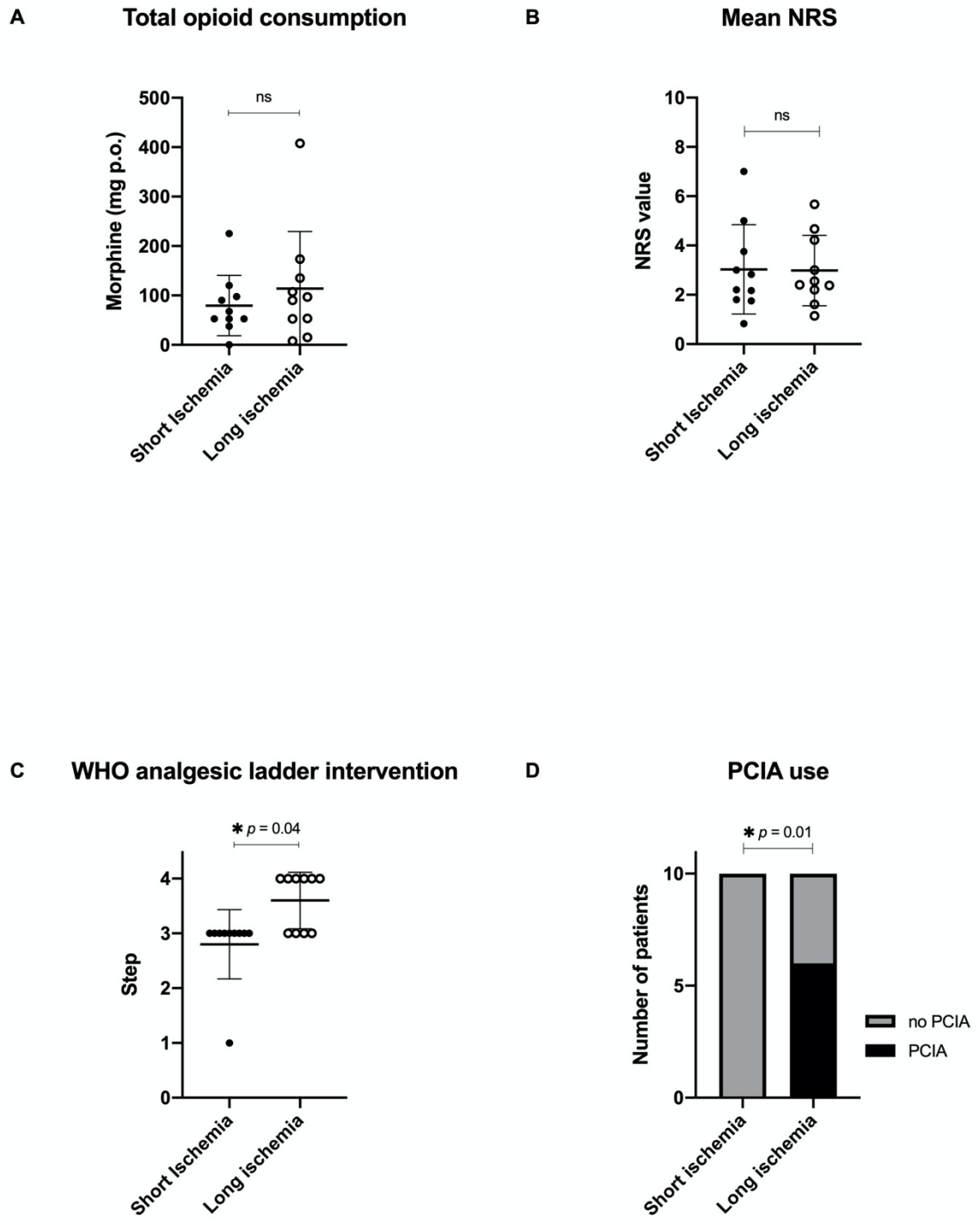

Fig. 2 Graphic illustration of secondary and tertiary outcomes

2A: Total Opioid consumption: The long ischemia group had a higher mean intake of mg p.o. morphine but showed no significance.
2B: Mean NRS in 48 postoperative hours showed no significant difference between both groups.
2C: Intervention according to the four-step WHO analgesic ladder was significantly higher in the long ischemia group compared to short ischemia group.
2D: In the long ischemia group significantly more patients required PCIA.

6 Discussion

In this study a total of twenty patients, either undergoing a long or short tourniquet induced ischemia during TKA, were compared regarding postoperative pain. The principle finding of this first interim analysis of twenty patients associated longer tourniquet time with more post-operative pain. A significantly higher intervention according to the four-step WHO analgesic ladder ($p = 0.04$) and significantly more patients requiring PCIA ($p < 0.01$) were found in the long ischemia group. There was also a trend to a higher total opioid consumption in the first 48 postoperative hours in the long ischemia group (113.9 mg p.o. morphine) compared to the short ischemia group (79.5 mg p.o. morphine), but this difference was not statistically significant. As intake of non-opioid analgesics did not show any difference between both groups, an opioid-sparing effect at this point of the study is very low. For further analysis co-analgesics should also be taken into account.

Interestingly the mean NRS in 48 p.op. hours showed no difference between both groups. Other studies have shown a higher pain score at postoperative day one and two.[30] What should also be taken into consideration is that Snyder et al found in a large cohort study where patients underwent oral surgery, that pain medication was a better indicator of patients pain than numerical pain scales.[31,32]

Our findings support the hypothesis that prolonged tourniquet time in TKA leads to more postoperative pain. This was also shown in the meta-analysis of Wang et al where tourniquet use only during cementation compared to long-duration tourniquet use resulted in less knee pain on the first post-operative day.[30]

Both groups were comparable in demographic characteristics in terms of age, sex, BMI and incidence of diabetes. The fact that preoperative intake of opioids was similar between both groups support the hypothesis that postoperative higher opioid consumption was due to the longer tourniquet time.

Regarding perioperative features there was no difference in terms of anaesthetic procedure, but a significantly higher mean tourniquet pressure was found in the long ischemia group. Surgeons are meant to adapt the tourniquet pressure to the systolic blood pressure prior to inflation. Even though the tourniquet pressure was higher in long ischemia group, mean of systolic blood pressures showed comparable means of 121 mmHg in the short vs. 125 mmHg in the long ischemia group ($p = 0.72$). As studies have made associations of higher tourniquet pressure to more postoperative pain, especially in lower limb surgery, differences between short and long ischemia group should be prevented.[33]

It should also be noted that all data was retrospectively collected using the digital medicine registration system i-pdos as a primary data source. That might increase the risk of inconsistent data registration. This was obviously the case for NRS. Collection of NRS values over 48 postoperative hours ranged between one and ten. NRS should be obtained every four to six hours, this would make a total of eight to twelve values and allow the comparison of groups at other time points (four, twelve, twenty-four hours postoperative) which might be beneficial in detecting differences in the peak of pain.

Another point that should be made is, that installation of PCIA take indications and contraindications into account. Not every patient is suitable for a PCIA even if he or she experiences severe pain. Decisions that led to, respectively prevented installation of a PCIA cannot always be found in the documentation.
Intervention according to the four-step WHO analgesic ladder and patients requiring PCIA were significantly higher in the long ischemia group. Both are not validated measurements at this point, are thus a potential source of detection bias and therefore limitation of this study.

This study has not made a direct association that longer tourniquet time goes along with more ischemia-reperfusion injury and therefore more postoperative pain. Future research applying similar tourniquet inflation pressures, as well as continuous recording of NRS is necessary to evaluate if longer tourniquet time influence postoperative pain outcomes. Taking systemic inflammation markers into account might make the link of postoperative pain due to higher I/R injury. Of course, a future study including muscle biopsy where e.g. antibody-deposition, complement-markers could be shown would be beneficial to investigate direct effect of I/R injury to postoperative pain.
This study was able to show that a longer tourniquet time in TKA resulted in a significantly higher postoperative pain-treatment according to the four-step WHO analgesic ladder and significantly more patients needing PCIA in 48 p.op. hours. There was a trend between longer tourniquet time and postoperative opioid consumption. No association was made between longer tourniquet time and higher NRS. The further twenty respectively forty patients might substantiate these findings.

7 Acknowledgments

I want to thank Robert Rieben for the great supervision and highly appreciated feedback. I also thank Mai Abd El Hafez for her support and her introduction to the project, Jane Shaw Boden for her help in academic writing and proofreading. A big thank you as well to Frank Klenke and Emanuel Liechti for their introduction to the i-pdos system and help in coping with patient's data.

I also want to express my gratitude to my parents to their encouragement and motivation. Many thanks to my flat-mate Fabienne for her kindness and going through this quarantine period with me. Finally, I want to thank everybody in the background supporting me.

8 Statuary declaration

“I herewith declare that I have composed the present thesis myself and without use of any other than the cited sources and aids. Sentences or parts of sentences quoted literally are marked as such; other references with regard to the statement and scope are indicated by full details of the publications concerned. The thesis in the same or similar form has not been submitted to any examination body and has not been published.”

14.5.2020, Studen BE

9 Attachments

10 Bibliography

1. Ethgen O, Bruyère O, Richy F, Dardennes C, Reginster J-Y. Health-Related Quality of Life in Total Hip and Total Knee Arthroplasty: A Qualitative and Systematic Review of the Literature. J Bone Jt Surg 2004;86(5):963–74.
2. Smith TO, Hing CB. A meta-analysis of tourniquet assisted arthroscopic knee surgery. The Knee 2009;16(5):317–21.
3. Tai T-W, Lin C-J, Jou I-M, Chang C-W, Lai K-A, Yang C-Y. Tourniquet use in total knee arthroplasty: a meta-analysis. Knee Surg Sports Traumatol Arthrosc 2010;19(7):1121–30.
4. Ejaz A, Laursen AC, Kappel A, Jakobsen T, Nielsen PT, Rasmussen S. Tourniquet induced ischemia and changes in metabolism during TKA: a randomized study using microdialysis. BMC Musculoskelet Disord 2015;16(1):326.
5. Kruse H, Christensen KP, Møller AM, Gögenur I. Tourniquet use during ankle surgery leads to increased postoperative opioid use. J Clin Anesth 2015;27(5):380–4.
6. Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. J Pathol 2000;190(3):255–66.
7. Becker L. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res 2004;61(3):461–70.
8. Diepenhorst GMP, van Gulik TM, Hack CE. Complement-Mediated Ischemia-Reperfusion Injury: Lessons Learned From Animal and Clinical Studies. Ann Surg 2009;249(6):889–99.
9. Zarbock A, Eroglu A, Erturk E, Ince C, Westphal M. Ischemia-Reperfusion Injury and Anesthesia. BioMed Res Int 2014;2014:1–3.
10. Stahl GL, Shernan SK, Smith PK, Levy JH. Complement Activation and Cardiac Surgery: A Novel Target for Improving Outcomes. Anesth Analg 2012;115(4):759–71.
11. Weiser MR, Williams JP, Moore FD, et al. Reperfusion injury of ischemic skeletal muscle is mediated by natural antibody and complement. J Exp Med 1996;183(5):2343–8.
12. Duehrkop C, Banz Y, Spirig R, et al. C1 Esterase Inhibitor Reduces Lower Extremity Ischemia/Reperfusion Injury and Associated Lung Damage. PLoS ONE 2013;8(8):e72059.
13. Mayer C, Franz A, Harmsen J-F, et al. Soft-tissue damage during total knee arthroplasty. J Orthop 2017;14(3):347–53.
14. Kumar N, Yadav C, Singh S, Kumar A, Vaithlingam A, Yadav S. Evaluation of pain in bilateral total knee replacement with and without tourniquet; a prospective randomized control trial. J Clin Orthop Trauma 2015;6(2):85–8.
15. Blaisdell F. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. Cardiovasc Surg 2002;10(6):620–30.
16. Raja Srinivasa. IASP's Proposed New Definition of Pain Released for Comment [Internet]. Int. Assoc. Study Pain. 2020;Available from: https://www.iasp-pain.org/Publications-News/NewsDetail.aspx?ItemNumber=9218
17. Zimmermann M, Rittmeister M. Postoperative Schmerztherapie in der Orthopädie. Orthop 2003;32(12):1110–9.
18. Kretz F-J, Schäffer J, Terboven T. Physiologie und Pathophysiologie des Schmerzes [Internet]. In: Anästhesie, Intensivmedizin, Notfallmedizin, Schmerztherapie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2016 [cited 2020 Mar 24]. p. 455–8.Available from: http://link.springer.com/10.1007/978-3-662-44771-0_41
19. Fact Sheet 3. Pathophysiology of Acute Pain.Brennan-Zahn_1485200016604_2.pdf.
20. Kretz F-J, Schäffer J, Terboven T. Spezielle Schmerztherapie [Internet]. In: Anästhesie, Intensivmedizin, Notfallmedizin, Schmerztherapie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2016 [cited 2020 Mar 24]. p. 473–83.Available from: http://link.springer.com/10.1007/978-3-662-44771-0_44
21. Simanski C, Neugebauer E. Postoperative Schmerztherapie. Chir 2003;74(3):254–75.
22. Kretz F-J, Schäffer J, Terboven T. Methoden der Schmerztherapie (mit palliativmedizinischem Schwerpunkt) [Internet]. In: Anästhesie, Intensivmedizin, Notfallmedizin, Schmerztherapie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2016 [cited 2020 Mar 24]. p. 461–71.Available from: http://link.springer.com/10.1007/978-3-662-44771-0_43

23. Mariano ER. Management of acute perioperative pain - UpToDate [Internet]. UpToDate. 2020 [cited 2020 Jan 29];Available from: https://www.uptodate.com/contents/management-of-acute-perioper…h_result&selectedTitle=4~150&usage_type=default&display_rank=4
24. Elmallah R, Chughtai M, Khlopas A, et al. Pain Control in Total Knee Arthroplasty. J Knee Surg 2017;31(06):504–13.
25. Tameem A. Analgesic ladders [Internet]. In: Plunkett E, Johnson E, Pierson A, editors. Returning to Work in Anaesthesia. Cambridge: Cambridge University Press; 2016 [cited 2020 May 4]. p. 315–7.Available from: https://www.cambridge.org/core/product/identifier/9781316227633%23CT-bp-32/type/book_part
26. Post-Operative Pain Management - PCA - Opioids - [Internet]. Teach Me Surg. [cited 2020 May 4];Available from: https://teachmesurgery.com/perioperative/general-complications/pain/
27. Fergusson D. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002;325(7365):652–4.
28. Treillet E, Laurent S, Hadjiat Y. Practical management of opioid rotation and equianalgesia. J Pain Res 2018;Volume 11:2587–601.
29. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. Arthritis Care Res 2011;63(S11):240–52.
30. Wang C, Zhou C, Qu H, Yan S, Pan Z. Comparison of tourniquet application only during cementation and long-duration tourniquet application in total knee arthroplasty: a meta-analysis. J Orthop Surg 2018;13(1):216.
31. Snyder M, Shugars DA, White RP, Phillips C. Pain Medication as an Indicator of Interference With Lifestyle and Oral Function During Recovery After Third Molar Surgery. J Oral Maxillofac Surg 2005;63(8):1130–7.
32. Rathod P, Deshmukh A, Robinson J, Greiz M, Ranawat A, Rodriguez J. Does Tourniquet Time in Primary Total Knee Arthroplasty Influence Clinical Recovery? J Knee Surg 2014;28(04):335–42.
33. Kam PCA, Kavanaugh R, Yoong FFY. The arterial tourniquet: pathophysiological consequences and anaesthetic implications. Anaesthesia 2001;56(6):534–45.