



Ischaemic Preconditioning in Total Knee Arthroplasty: A Randomized Controlled Trial

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Abstract

Introduction: Reducing pain post-operatively after a Total knee arthroplasty (TKA) can be a challenging problem. Non-pharmacological approaches have infrequently been explored. Ischemic preconditioning (ICP) of tissue before undergoing a total knee replacement may reduce pain and subsequently improve patient satisfaction.

Methods: We enrolled 96 patients undergoing unilateral TKA. Forty-five patients were randomized to undergo ICP. All patients were assessed pre-operatively, on postoperative day 2 and at 6 weeks following surgery. We calculated the Visual Analog Scale (VAS), Knee Society Score (KSS), Quadriceps strength and range of motion at each interval.

Results: No differences were found between the treatment and control group at each interval. VAS score preoperatively: p-value 0.711(-0.050-0.074); postoperative day 2: p-value 0.126(-0.013-0.105); and postoperative week 6: p-value 0.615(-0.039-0.066). This was similar for the KSS preoperative: p-value 0.788(-0.054 - 0.071); and at 6 weeks: p-value 0.472(-0.036-0.077). Preoperative flexion and extension values showed comparable results: p-value 0.855(-0.047-0.057); postoperative day two: p-value 0.27 (-0.023-0.082); and postoperative week 6: p-value 0.785 (-0.060-0.045).

Conclusion: Ischemic preconditioning did not demonstrate any clinical significant improvement in the VAS pain score, KSS and flexion and extension values after a unilateral total knee arthroplasty.

Keywords: Total Knee Arthroplasty; Ischaemic Preconditioning; Limb Preconditioning; Patient satisfaction; Postoperative Pain

Introduction

Postoperative pain control continues to be one of the challenges faced after a total knee arthroplasty. With the increased number of total knee arthroplasties on the rise, this will become an even larger concern [1]. Historically, total knee arthroplasties have been associated with severe pain, which led to prolonged inpatient hospitalization and extended recovery times. Multiple advances have been made over the years to try to maximize function while minimizing pain. These modalities included preoperative medical optimization, accelerated rehabilitation protocols, improved peri-operative pain management strategies and improved surgical technique [2, 3].

Non-pharmacologic approaches to reduce pain postoperatively remain rare [4]. Ischemic preconditioning has been proposed as a possible way to decrease pain postoperatively [5-11]. Re-perfusion has been shown to result in a local and systemic inflammatory response that could exacerbate tissue injury in addition to that caused by the ischemia alone. Free radicals are released after deflation of the tourniquet [12-15]. These free radicals can cause cardiorespiratory and neurological complications [16-18]. The resultant cellular damage that occurs after re-perfusion of previously healthy tissue is termed "ischemia-re-perfusion injury" [9].

Ischemic preconditioning in animal models has demonstrated a tolerance in tissues following prolonged ischemia with tourniquet use. This was achieved by subjecting the tissues to a short period of ischemia followed by re-perfusion, prior to prolonged usage of a tourniquet [7]. (The technique entails: inflation of the tourniquet for a brief duration, followed by deflating the tourniquet for a certain period of time to allow re-perfusion, before inflating the tourniquet for a second time at the beginning of the surgery). Theoretically this leads to increase tolerance of the tissues to ischemia, which in turn will reduce oxidative stress, inflammation and apoptosis. Despite the proposed advantage of ischemic preconditioning, it is not without risks [19, 20] as demonstrated by increased nerve degeneration, loss of pain sensation and motor function seen in rats [8].

Most of the clinical trials conducted for the benefits of ischemic preconditioning evaluated kidney and heart models in animals with only a few studies looking at the effects on skeletal muscle during a total knee arthroplasty [12, 21-25]. Different studies comparing ischemic preconditioning for a routine total knee arthroplasty, have evaluated postoperative pain, inflammatory markers and hospital stay to demonstrate improved outcomes. Two studies assessing inflammatory markers did not see a significant difference between the groups but both demonstrated a decrease in pain in the ischemic preconditioning groups. With regards to the length of hospitalization there were conflicting results. One study [5] showed no difference while the other study demonstrated a shorter hospital stay [4] in the ischemic preconditioning group [4, 5]. Sha et al. [11] assessed the genomic response from ICP from muscle biopsies. They

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found that ICP induces a protective genomic response in the tissues of those patients undergoing a TKA.

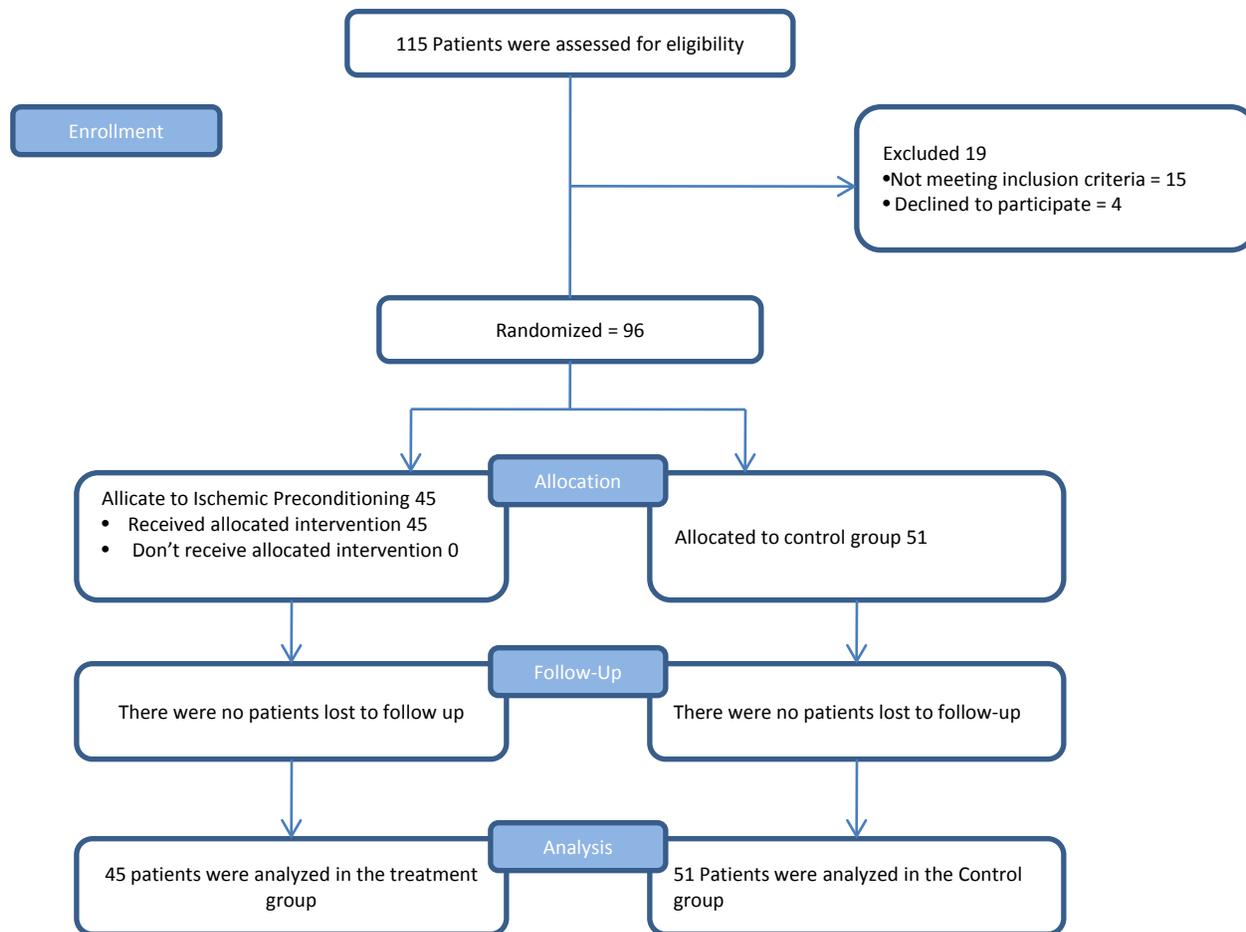
The goal of our study was to evaluate if ischemic preconditioning does indeed decrease pain postoperatively which could lead to a better early functional outcome and greater patient satisfaction. We also looked at the Knee Society Score (KSS) and knee range of motion (ROM) in both the treatment and control group.

Patients and Methods

After we obtained ethics approval (Bio #: 15-264) we enrolled 96 patients undergoing unilateral total knee arthroplasty [Figure 1]. Patients were enrolled between 2016 and 2017. All the patients that were included received their surgery at our tertiary institution. Patients were randomized once we obtained written consent by using their hospitalization number. Patients with an even hospital number were assigned to the treatment group (45 patients) and patients with an uneven hospital number were assigned to the control group (51 patients). We enrolled 96 patients on an intention to treat basis. Patients were blinded to the procedure, as were the physiotherapists and nursing staff recording the VAS pain score and assessing for quadriceps strength and range of motion. Pre-operatively the operating surgeon calculated the VAS-score (pain score according to a 10 point visual analog scale, with 0 indicating no pain and 10 indicating

the most severe pain), the Knee Society Score (KSS), range of motion of the knee and the quadriceps function. All the patients subsequently underwent a spinal anesthetic and a femoral nerve block before being taken into the operating room. If there was a contraindication to a spinal anesthetic or a femoral nerve block (bleeding disorder, previous spinal surgery, patient's wishes), then the patient was simply excluded from the study. This enabled us to minimize confounding variables. A tourniquet was applied to the operated thigh in all the cases once the patients entered the operating room. In the treatment group the tourniquet on the surgical leg was inflated to 250 mmHg for 5 minutes. The tourniquet was then deflated once the alarm sounded, to allow re-perfusion. The tourniquet was left deflated for at least another 5 minutes before skin incision and re-inflation. During this time of deflation the surgical leg was prepped and draped.

In the control group the tourniquet on the surgical leg was left deflated until the skin incision but another non-attached tourniquet was inflated for 5 minutes. The aforementioned tourniquet was applied around a tensor bandage and was thus not attached to the patient. It was deliberately performed so that the patients in both the control group and the treatment group heard the inflation and deflation of the tourniquet prior to the actual surgical incision as part of our blinding technique. For both groups the tourniquet was then inflated once the skin incision was made and deflated once the cement



hardened after component placement. We used a medial Para patellar approached with a combined gap balancing and measured resection technique in all the cases.

All the patients were admitted to the surgical ward where the VAS score was performed by the nursing staff on postoperative day two. By obtaining the VAS-score POD 2 it allowed ample time for the effects of the femoral nerve block to resolve. The physiotherapists assessed the range of motion and the quadriceps function of the operated leg, on postoperative day two. At six weeks from the surgical date the VAS-score, KSS score, the range of motion and quadriceps function were measured by the operating surgeon in their office, during a schedule follow up visit.

Statistics

An independent statistician determined that our study was adequately powered. Differences in scores of both the control and treatment procedures were compared using 95% confidence intervals with respect to binomial distribution. The corresponding p-values were calculated using the classical normal approximation method.

Results

Ninety-six patients were enrolled [Table 1]. Fifty-six were female and forty were male. Forty three total knees were on the left and fifty three were on the right [Table 2]. Severity of osteoarthritis was rated as severe according to the Outer bridge classification in the medial tibio-femoral compartment in 72 patients. In nine patients it was severe in the lateral tibio-femoral compartment, in three patients in the patellofemoral compartment alone, in five patients in the medial and patellofemoral compartment and in seven patients in the medial-and-lateral tibiofemoral compartment. When the VAS scores were compared preoperatively between groups: p-value 0.711(-0.050-0.074); postoperative day 2: p-value 0.126(-0.013-0.105); and postoperative week 6: p-value 0.615(-0.039-0.066), there was no significant difference in the outcome [Figure 2].

Table 1: VAS - Visual Analog Scale; KSS -Knee Society Score; POD - Post-operative

	Control Group	Treatment Group	P-Value
Median Preoperative VAS score	5.9	5.7	0.711(-0.050-0.074)
Median VAS score POD 2	3.5	3.1	0.126(-0.013-0.105)
Median VAS score 6 weeks postoperative	2.3	2.1	0.615(-0.039-0.066)
KSS Preoperatively (Objective knee score/ Functional score)	56.1/53.6	57/53.5	0.788(-0.054 - 0.071)
KSS 6 weeks postoperative (Objective knee Score/Functional score)	71.5/60	73.6/56.7	0.472(-0.036-0.077)

Table 2: OA - Osteoarthritis; POD - Postoperative day

	Control Group	Treatment Group
Patients -Male	22	18
Patients - Female	29	27
Right knee Arthroplasty	20	23
Left knee Arthroplasty	21	22
Median Tourniquet Time	47	45
Quadriceps Function POD 2	2.5	2.5
Medial compartment OA	35	36
Lateral compartment OA	4	4
Medial and lateral compartment OA	6	1
Patellofemoral compartment	1	2
Medial and Patellofemoral compartment	4	2
Lateral and Patellofemoral compartment	1	0

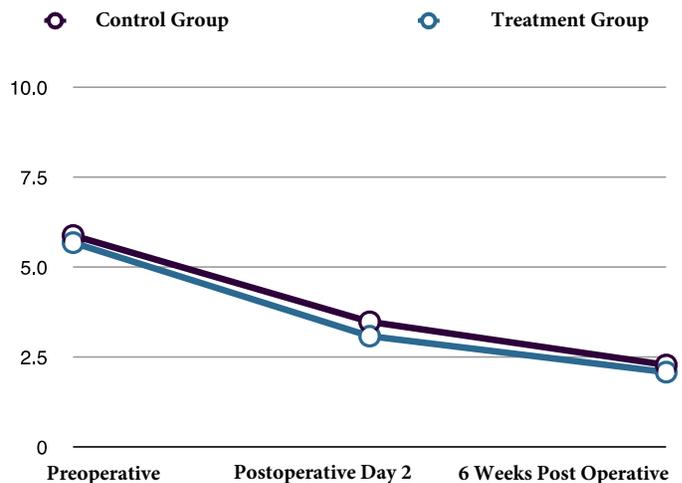


Figure 2: VAS score between the treatment group (Ischemic preconditioning) and the control group.

When comparing the KSS preoperatively: p-value 0.788(-0.054 - 0.071); and at 6 weeks: p-value 0.472(-0.036-0.077) there was no significant difference noted [Figure 2]. This was also true for the preoperative flexion and extension values preoperative: p-value 0.855 (-0.047-0.057); postoperatively day two: p-value 0.27 (-0.023-0.082); and postoperatively week 6: p-value 0.785 (-0.060-0.045).

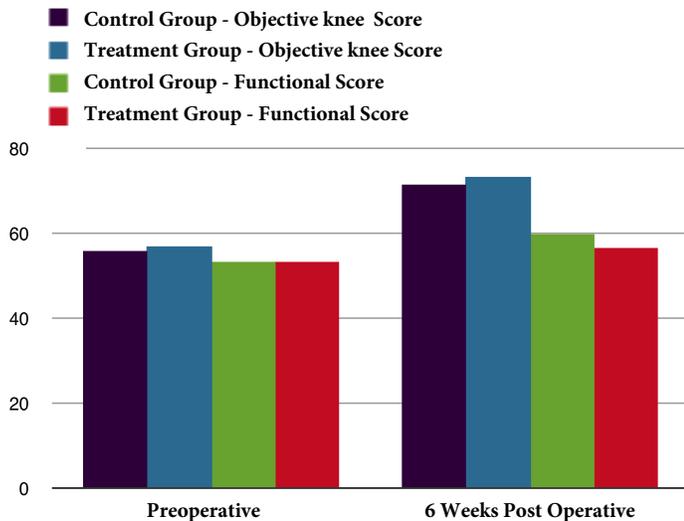


Figure 3: Comparing the Knee society score pre-operatively to 6 weeks post-operative

Discussion

Postoperative pain management after a total knee arthroplasty remains a complex challenge surrounding total knee arthroplasty. Many modalities are currently being employed to control pain, which theoretically will lead to improved early function and patient satisfaction [26, 27].

It is still unknown how ICP reduces pain. Multiple theories have emerged including the notion that ICP reduces inflammation and swelling [4]. This has been proven in rats [28], but has not been demonstrated in humans undergoing total knee surgery [4]. In addition to decreased inflammation, a reduction in bleeding has been observed. This phenomenon was thought to be due to the decreased inflammation, which is known to impair normal hemostasis [21, 29]. Interestingly no clinical significant results have been demonstrated in relation to serologic levels of inflammatory markers or systemic markers of procoagulation [5, 6, 10, 21].

There are conflicting findings regarding length of hospital stay between studies with one study demonstrating a reduced length of stay with ischemic preconditioning [10] although there were no differences in analgesia consumption or changes in inflammatory markers [5, 10, 21].

We did not demonstrate a clear advantage when performing preconditioning in unilateral knee replacement for osteoarthritis. There was however a slight trend of improved VAS scores and knee flexion and extension values postoperative day two for the group that was selected for ischemic preconditioning. This did not reach statistical significance. The results were different from previous reports where a statistically significant difference was seen in favour of ischemic preconditioning when looking at postoperative pain (at rest and with exercise) [5, 10]. In the aforesaid studies the effect size was small and patients did receive epidural analgesia, which is known to positively influence the perioperative inflammatory response. Memtsoudis et al's [5] administered Propofol to all their patients for sedation during the procedure. Propofol has antioxidant properties, which could influence the results [9, 30-34]. Propofol was administered to the control and treatment group in all cases in their study, which certainly will eliminate any bias between the groups. This can explain

why there were no serological differences found in their study. In our study we did not account for Propofol administration for sedation during the total knee arthroplasty, and therefore that might explain why we did not see a clinical significant difference between the control and treatment group.

ICP is thought to lessen the magnitude of the re-perfusion injury after an ischemic event elsewhere in the body [35]. We have not accounted for patients with ischemic heart disease or renal ischemia. Certainly by having this pre-existing condition, patients will have a degree of ICP on board and this could alter the results. Future studies could exclude these patients and eliminate these co-variables. However, with our randomization process, one would consider both groups to be equally affected and therefore shouldn't influence the results.

There are several limitations to our study. Firstly, we evaluated the VAS pain score values pre operatively and postoperative day two. The VAS values postoperative day two gives a point measure and not a complete representation of the patient's overall hospital stay (POD 1-3). We purposely chose postoperative day two so that there would be no residual effect left from the regional and spinal anesthetic, while pain measures were taken. In addition the VAS scores were collected at routine intervals postoperative day two by the nursing staff as per their protocol. The median VAS score was then calculated and used. This method allowed us to use the median value over a 24-hour period, rather than a single value that might be artificially magnified due to certain events (returning from physiotherapy, delayed in receiving analgesia etc.). We feared that by measuring the VAS scores on postoperative day 3, we could end up with incomplete data as a large majority of our patients are discharged on day three. Secondly, we did not look at the inflammatory markers, which might shed light on whether differences in inflammation markers were related to disparities in pain levels. In previous studies there were no differences observed in the inflammatory markers and therefore it was not our goal to replicate these findings [5, 10, 17, 21].

Thirdly: we have only looked at ischemic preconditioning performed for 5 minutes prior to surgery. There are multiple ways to perform ischemic preconditioning which could alter our results. We decided to use 5 minutes prior to surgery, based on the description of techniques used in previous studies.

The fourth limitation is that two fellowship trained adult reconstruction surgeons performed the surgeries in all the cases. Even though we tried to perform our surgeries similarly, there will be differences in technique, which could lead to differences in outcome. By having only adult reconstruction surgeons perform all the surgeries it will positively limit confounding factors in technique, but adversely make it less applicable to the general orthopaedic surgeon.

Lastly we did not look at postoperative cognitive dysfunction (POCD). In the elderly population cognitive dysfunction can be devastating for the patients as well as their families. Ischemic preconditioning has been shown to reduce POCD by improving pulmonary function, which leads to better pulmonary oxygenation and subsequently better cerebral oxygenation [21, 36-38]. This is an area worth exploring for future studies.

In conclusion, ischemic preconditioning did not demonstrate any clinical significant improvement in the VAS pain score, KSS and flexion and extension values after a unilateral total knee arthroplasty. There are other beneficial effects with performing IPC, and with little associated risk, can be safely performed on selected patients.

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