International Journal of Research in Orthopaedics
Dubey RR et al. Int J Res Orthop. 2019 Nov;5(6):1000-1004
http://www.ijoro.org

DOI: http://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20194173

Original Research Article

Does ischemic preconditioning preoperatively reduce postoperative pain and analgesic requirement in total knee arthroplasty?

Rajiv Ranjan Dubey[1]*, Bhabani Shankar Behera[2], Manish Prasad[1]

[1]Department of Orthopaedics, Armed Forces Medical College, Pune, Maharashtra, India
[2]Department of Orthopaedics, Railway Hospital, Khurda Road, Odisha, India

Received: 20 August 2019
Revised: 03 September 2019
Accepted: 06 September 2019

***Correspondence:**
Dr. Rajiv Ranjan Dubey,
E-mail: dr.rajiv.afmc@gmail.com

ABSTRACT

Background: Osteoarthritis of knee is one of the most commonly affecting condition affecting the activities of daily living in the middle age group Indian and Asian population. Total knee arthroplasty (TKA) performed for pain relief and improvement in mobility of individuals is associated with significant post-operative pain. Ischemic preconditioning is one of the non-pharmacologic methods of reduction in postoperative pain using variable periods of tourniquet induced ischaemia which has limited data in literature.
Methods: Sample size (n=30) was taken. A standard automatic pneumatic tourniquet was used while performing ischemic preconditioning of the limb prior to TKA and during surgery. Statistical analysis was performed with p values <0.05 considered significant. Standard postoperative analgesia as per hospital protocol was given to patients.
Results: The mean 6 hour postoperative and 48-hr postoperative visual analogue scale (VAS) score at rest is significantly higher compared to mean preoperative VAS score at rest ($p<0.01$ for both). The distribution of mean preoperative and 24 hour postoperative VAS score at rest did not differ significantly ($p>0.05$). The mean % change in postoperative period compared to preoperative VAS at rest was 47.06%.
Conclusions: In this study, the effect of preconditioning over postoperative pain relief was not consistent. Although the patient reported pain scores were low at 6th and 24th postoperative hour, the effect at 48th postoperative hour was not satisfactory. Studies with larger sample size required for better understanding of ischemic preconditioning.

Keywords: Scheming preconditioning, Tourniquet, Total knee arthroplasty, Visual analogue score

INTRODUCTION

Osteoarthritis (OA) of knee is a degenerative disorder characterized by the softening, ulceration and focal loss of articular cartilage, sclerosis of the subchondral bone, marginal osteophyte formation and a range of morphological and biochemical changes in the synovium and capsule of the knee joint. It clinically presents with pain on activity and stiffness. When no known cause is found it is referred as primary OA of knee.[1] In Indian scenario the prevalence ranges from 22%-39%; the prevalence being directly proportional to the ageing population.[1] Total knee arthroplasty (TKA) has been a successful surgical procedure for advanced arthritis of the knee.

TKA surgery can be associated with considerable postoperative pain.[2] A pneumatic tourniquet is commonly used in TKA surgery to improve surgical field visualisation and to decrease the operating time. The bloodless operating field also improves bone cement interface thus preventing component loosening in a cemented TKA. However, the use of tourniquet may result in more postoperative pain and may delay the

recovery in comparison to a surgery done without tourniquet.[3,4] Further, even with the introduction of multimodal analgesia as post-operative pain relief measure in modern TKA surgery, literature is deficient for a method that can be both non pharmacological as well as noninvasive.[5] Ischemic preconditioning (IPC) in various tissue models has been shown as a phenomenon by which a tissue, when subjected to short periods of ischemia, behaves to be more tolerant to a longer period of ischemia and reperfusion injury.[5,6] However, the application of IPC in major orthopedic surgery like TKA is limited till date with very few studies studying the effect of ischemic preconditioning as a method of analgesia.[7,8]

This study was undertaken with an aim to study the effect of ischemic preconditioning on post-operative pain relief in patients undergoing TKA by measuring patient reported pain score, postoperative requirement of analgesia, period required for ambulation along with duration of hospitalization.

METHODS

This was a prospective observational cohort study conducted on 30 cases of unilateral TKAs conducted between November 2015 to September 2017 were considered for the study after fulfilling the inclusion and exclusion criteria at Armed Forces Medical College, Pune.

All the surgeries were performed by the senior surgeons. All the patients were given combined spinal-epidural anesthesia (12.5 mg bupivacaine 0.5%), following which a preconditioning protocol was followed, that consisted of three 'five-minute' periods of pneumatic tourniquet insufflations on the upper thigh of operative limb, interrupted by five-minute periods of reperfusion. Following this, the operative limb was exsanguinated and the tourniquet was again inflated and TKA performed. To avoid delay in surgery, preconditioning was performed during cleaning and draping of the patient. Postoperative pain management consisted of epidural infusion of 0.125% bupivacaine with a basal rate of 4 mL, a demand dose of bolus 4 ml, and a lockout of 10 minutes. The epidural catheters were removed in afternoon following the 2nd postoperative day. All the patients were made available with injection paracetamol 1 g every 8 hourly with additional dose kept on demand (maximum up to 5 grams per day). Injection diclofenac 75 mg was made available as additional pain relief. The net amount of epidural infusion was recorded as well as the total intake of paracetamol and diclofenac. Patient demographics including age, sex, and body mass index; perioperative data including tourniquet time during surgery, the volume of fluid administered during 48 hour post-operative period was recorded. For thromboprophylaxis, all the patients were administered injection low molecular weight heparin at a dose of 1 mg/kg body weight on the evening prior to surgery and then from the first postoperative day, morning daily doses were administered till discharge. Visual analogue scale (VAS) score was recorded in each patient preoperatively as well as 6th hour, 24th hour and 48th hour post operatively both during rest and with 45° knee flexion. The net epidural volume and analgesic intake was recorded during initial 48 hour postoperatively. The periarticular circumference (girth of the thigh at the midpoint between superior pole of patella and anterior superior iliac spine) was measured preoperatively and at 48th hour post operatively. All the patients underwent same postoperative rehabilitation that consisted of knee range of motion exercises started in early postoperative period and walker assisted full weight bearing ambulation from the first postoperative day. The duration of hospitalization; time taken to reach few physical therapy milestones (i.e. independently when the patient can transfer himself from sitting position to wheelchair and back, patient's ability to ambulate 40 feet with a walking frame) were also recorded.

Inclusion criteria

This study included patients with primary osteoarthritis of the knee.

Exclusion criteria

Primary osteoarthritis of knee with severe deformities such as varus deformity more than 15 degree and fixed flexion deformity more than 20 degree, previous surgery on the affected knee, inflammatory arthritis of the knee, revision knee arthroplasty, previous history of injection of intra articular steroid or any viscosupplementation in the affected knee within six weeks of index total knee arthroplasty, immunocompromised patients, patients with peripheral vascular diseases in the affected limb, patients with deranged coagulation profile, patients operated under general anaesthesia.

Statistical methods

The data on categorical variables are shown as n (% of cases) and data on continuous variables are shown as mean±standard deviation (SD) across all follow-ups. The intra-group pair-wise comparison of continuous variables is done using the paired t-test. The underlying normality assumption is confirmed before subjecting the study variables to t-test. In the entire study, the p values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS version 21.0, IBM Corporation, USA) for MS Windows.

RESULTS

A total of 30 patients were included in the study after fulfilling the above- mentioned inclusion and exclusion criteria. 17 male subjects and 13 female subjects were

included in the study with a mean age 65.43 years (range: 54.0-78.0 years). The mean body mass index was 25.15 kg/m² (range: 19.0-30.0 kg/m²) (Table 1).

Table 1: Distribution of cases studied according to BMI group.

BMI groups (kg/m^2)	No. of cases	% of cases
Underweight (<18.5)	0	0.0
Normal (18.5-22.9)	5	16.7
Overweight (23.0-24.9)	7	23.3
Pre-obese (25.0-29.9)	17	56.7
Obese type 1 (30.0-40.0)	1	3.3
Total	30	100.0

Table 2: The comparison of preoperative and postoperative pain scores (VAS) (n=30).

	VAS score at rest		VAS score at knee flexion	
Follow-up	**Mean**	**SD**	**Mean**	**SD**
Preoperative	0.73	0.74	1.77	0.63
6-hr postoperative	1.37	0.81	1.50	1.22
24-hr postoperative	1.07	0.74	2.13	0.90
48-hr postoperative	1.57	0.97	2.53	1.07
% change at 48-hr postoperative	47.06%	--	57.78%	--
P value (pair-wise)				
Preoperativevs. 6-hr postoperative	0.004**		0.318NS	
Preoperative vs. 24-hr postoperative	0.086NS		0.062NS	
Preoperative vs. 48-hr postoperative	0.001***		0.001***	

Values are mean and standard deviation (SD). P values by paired t test. P<0.05 is considered to be statistically significant. (*p<0.05, **p<0.01, ***p<0.001), NS- statistically not significant.

The distribution of mean 6-hr postoperative and 48-hr postoperative VAS score at rest is significantly higher compared to mean preoperative VAS score at rest (p<0.01 for both). The distribution of mean pre-op and 24-hr post-op VAS score at rest did not differ significantly (p>0.05). The mean% change at 48-hr postoperative compared to pre-op in VAS score at rest is 47.06% (Table 2).

Table 3: The comparison of preoperative and postoperative periarticular circumference (n=30).

	Periarticular circumference	
Follow-up	**Mean**	**SD**
Pre-op	50.07	6.11
48-hr postoperative	51.41	6.26
% change at 48-hr post-op	2.67%	--
P value (pair-wise)		
Preoperative vs. 48-hr postoperative	0.001***	

The values are mean and standard deviation (SD). P values by Paired t test. P<0.05 is considered to be statistically significant. (*p<0.05, **p<0.01, ***p<0.001), NS- statistically non-significant.

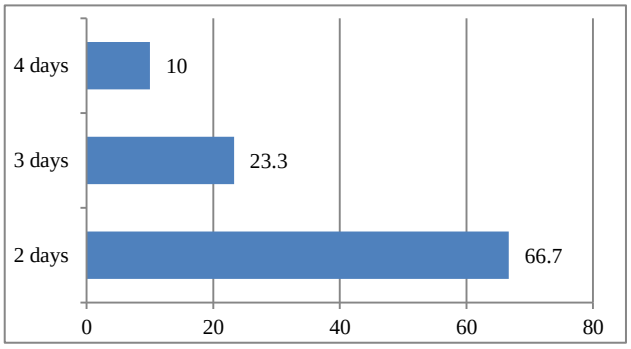

Figure 1: The distribution of postoperative time taken to ambulate (40 feet) with walker.

Table 4: The descriptive statistics of the overall analgesic's intake and total isotonic IV fluid administered within first 48 hrs postoperatively.

Intervention within 48-hrs postoperatively	Mean	SD	Median	Minimum	Maximum
Overall epidural infusion of bupivacaine (ml)	36.00	3.96	36.00	30.00	44.00
Overall intake of Inj. paracetamol (gm)	6.05	1.32	6.00	4.00	8.00
Overall intake of Inj. diclofenac (mg)	171.67	82.72	150.00	0.00	300.00
Total isotonic intravenous fluid administered (ml)	1236.33	183.18	1200.00	900.00	1600.00

The distribution of mean 48-hr postoperative periarticular circumference is significantly higher compared to mean preoperative periarticular circumference (p<0.001). The mean% change at 48-hr post-op compared to pre-op in periarticular circumference is 2.67% (Table 3). The mean±SD of length of hospital stay of the entire group of cases studied was 5.33±0.76 days (Figure 1). The mean±SD of tourniquet time of the entire group of cases studied was 88.57±8.26 mins, the minimum-maximum range of tourniquet time was 75-108 mins. The mean±SD of time taken for independent transfer for the entire group of cases studied was 3.53±0.73 days, the minimum - maximum range of time to independent transfer was 3-5 days (Figure 2). The mean±SD of time taken for independent transfer for the entire group of cases studied was 3.53±0.73 days, the minimum - maximum range of time to independent transfer was 3-5 days (Figure 2). The descriptive statistics of the overall analgesics intake and

total isotonic IV fluid administered within first 48-hrs post-operatively are as shown in Table 4.

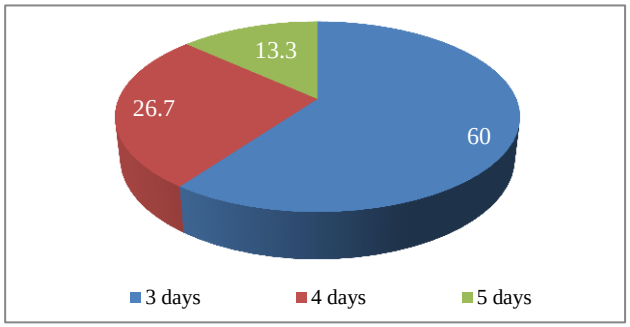

Figure 2: Distribution of time taken for independent transfer.

DISCUSSION

Memtsoudis et al, in a similar study had chosen a 5 minutes period of ischemia based on their past experience; however, we have chosen three spells of 5 minutes period for limb ischemia with an intention to have a more pronounced effect of preconditioning.[7] In this study, we have found that the distribution of mean 48-hour post-operative VAS score at knee flexion is significantly higher compared to mean pre-operative VAS score at knee flexion ($p<0.001$). However, the distribution of mean preoperative and 6th hour post-operative as well as preoperative and 24th hour post-operative VAS score at knee flexion did not differ significantly ($p>0.05$ for both). The mean% change at 48th hour post-op compared to pre-op in VAS score at knee flexion is 57.78%. Considering that the pain scores are consistently higher during immediate postoperative period in an arthroplasty surgery, with the multimodal analgesia used in our study population showed no significant difference in patient-reported pain scores between preoperatively and at 6th and 24th hour postoperatively. This can be attributed to a satisfactory analgesia effect within first 24 hours. Hence, our results correlate with the previous investigator's finding that the preconditioning may be associated with less pain postoperatively after a total knee arthroplasty surgery. But, the significant difference in preoperative and 48th hour post-operative pain score shows that the analgesia effect is not consistent at a later period like 48th hour. In a prospective randomized study by Memtsoudis et al, with a total 60 patients (30 in the preconditioning group and 30 in the non-preconditioning group or control group) have found that there was a significant less postoperative pain in comparison to a control group.[7] However, in that study different strategy of limb preconditioning as well as different multimodal postoperative analgesia was used. They used only one 5 minute period of tourniquet inflation followed by release and patients also received intraoperative femoral nerve blocks with 0.25% bupivacaine and epinephrine in strength of 1:200,000. But, in our study, we had subjected the patients to three 5 minutes period of ischemia as mentioned above and no regional anesthesia like femoral nerve block was used. The regional anesthesia can influence the postoperative inflammatory response and which may influence the effect of limb preconditioning on pain response in these setting. The mean±SD of overall epidural infusion of bupivacaine in the study group is 36.00±3.96 ml and minimum - maximum dose was 30.00-44.00 ml within 48th hr post-operatively. In the above randomized study, however the total volume of epidural analgesics administered was 140.5±68.4 ml (preconditioning group) and 160.8±70.1 ml (control group) and authors couldn't observe any significant difference ($p=0.432$) in a total amount of epidural analgesic intake between two groups.[7] This difference in epidural intake can be attributed to different analgesics protocol followed in our study. In the aforementioned study, researchers have used both bupivacaine and hydromorphone via an epidural catheter in addition to intraoperative femoral nerve block. However, in our study different postoperative analgesia was used with both injection paracetamol and diclofenac. The mean±SD of overall intake of inj paracetamol in the study group is 6.05±1.32 gm and minimum-maximum intake was 4.00-8.00 gm within 48th hr postoperatively. The mean±SD of overall intake of inj. diclofenac in the study group is 171.67±82.72 mg and minimum-maximum intake was 0.00-300.00 mg within 48th hr postoperatively. This different analgesia was used as per institutional protocol. The mean±SD of overall total isotonic intravenous fluid administered in the study group is 1236.33±183.18 ml and minimum-maximum intravenous fluid administration was 900.00-1600.00 ml within 48th hr postoperatively. The mean±SD of the duration of tourniquet during surgery of the entire group of cases studied was 88.57±8.26 mins, the minimum-maximum range of duration of tourniquet time was 75-108 mins. In terms of median/ interquartile range (IQR) in our study, the tourniquet time was 88.5 mins/12 min and volume of isotonic fluid administered within first 48 hr postoperatively was 1200 ml/250 ml. In the previous study the researchers have found median/IQR of fluid intake as 1700 ml/500 ml and tourniquet time 47.5 mins/13.3 mins in the preconditioning group.[7] This difference in result can be attributed to application of tourniquet till implantation of cemented components in their study, whereas in our study it has been applied till the end of surgery and application of compression dressings

The duration of hospitalization (mean±SD) was 5.33±0.76 days in our study population. There was no adverse event recorded during the hospital stay in any of the patient. The criteria for discharge was the achievement of various physical therapy milestones including active knee range of motion at least 10-90 degrees, independent transfers, and ambulation up to a minimum 40 feet with walking frame support. In the previous study hospitalization length was found to be 108±39 hours (4.5±1.6 days) in preconditioning group and the effect of preconditioning had no significant influence over the duration of hospital stay.[7] The

difference in hospitalization duration could be due to the criteria for discharge followed in our study.

The mean±SD of time taken to ambulate up to 40 feet with walker support for the entire group of cases in our study was 2.43±0.68 days and the time taken for independent transfer for the entire group of cases studied was 3.53±0.73 days. In terms of median/IQR (Interquartile range), our results are 2.0 days/1.0 for ambulation up to 40 feet 3.0days/1.0 for independent transfer. In a previous study the duration to achieve ambulation up to 40 feet was achieved with 2.0 days/1.0 (median/IQR) versus 3.0/1.0 in preconditioning versus control group respectively. But the investigators couldn't find any significant difference in both groups.[7] The study didn't mention the pain management strategy after 48th hour, as these physical therapy milestones can be delayed by the patient's discomfort leading to lack of activity and inadequate physiotherapy

Limitations of the study

The study has many limitations including a small sample size for which extrapolation of the result into a general population is difficult. Therefore, a larger population-based prospective randomized comparative study may be designed to elaborate the effects of ischemic preconditioning in TKA surgery to derive a firm conclusion.

CONCLUSION

The postoperative pain control in a TKA surgery has been a challenge for the orthopedic surgeon. In spite of the intervention of multimodal analgesia, a combined approach of using a non-pharmacological and non-invasive method with other pharmacological agents is still evolving. Few studies in the literature that have made observations regarding the effects of ischemic limb preconditioning in patients who underwent TKA, none of them being studied in any Asian population. In this study, the effect of preconditioning over postoperative pain relief was not consistent. Although the patient reported pain scores were low at 6th and 24th postoperative hour, the effect at 48th postoperative hour was not satisfactory. To conclude, proper patient selection and proper counseling prior to a knee arthroplasty surgery is important to achieve a long-term patient satisfaction. In spite of the shortcoming of our study, the fact that the literature is lacking enough studies regarding the utility of limb preconditioning in TKA, the data generated out of our study population can be used for conducting further multicenter trials in future.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Dubey RR, Behera BS, Prasad M. Does ischemic preconditioning preoperatively reduce postoperative pain and analgesic requirement in total knee arthroplasty?. Int J Res Orthop 2019;5:1000-4.