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ORIGINAL STUDY

Local Infiltration Analgesia reduces pain and hospital stay after primary TKA : randomized controlled double blind trial

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Postoperative analgesia following Total Knee Arthroplasty (TKA) with the use of parenteral opioids or epidural analgesia can be associated with important side effects. Good perioperative analgesia facilitates faster rehabilitation, improves patient satisfaction, and may reduce the hospital stay. We investigated the analgesic effect of a locally injected mixture of drugs, in a double blinded RCT in 80 primary TKA. They were randomized either to receive a periarticular mixture of drugs containing bupivacaine, ketorolac, morphine, and adrenalline or to receive normal saline. Visual analog scores (VAS) for pain (at rest and during activity) and for patient satisfaction and range of motion were recorded postoperatively. The patients who had received the periarticular injection used significantly less the Patient Controlled Analgesia (PCA) after the surgery as compared to the control group. In addition, they had lower VAS for pain during rest and activity and higher visual analog scores for patient satisfaction 72 hours postoperatively. No major complication related to the drugs was observed. Intraoperative periarticular injection with multimodal drugs following TKA can significantly reduce the postoperative pain and hence the requirements for PCA and hospital stay, with no apparent risks.

Keywords : Total Knee Arthroplasty (TKA) ; Local Infiltration Analgesia (LIA) ; pain ; Patient Controlled Analgesia (PCA) ; knee.

INTRODUCTION

Total Knee Arthroplasty (TKA) is a commonly performed surgical procedure, all across the world. Its popularity and acceptance is increasing exponentially, due to long term successful outcome. However, TKA may be associated with severe postoperative pain, usually requiring prolonged hospitalization to provide effective analgesia. This prolonged hospital stay and relative immobilization of the patient may cause unwanted medical problems like nosocomial infection, deep vein thrombosis (DVT) and poor surgical outcome. Adequate management of postoperative pain following TKA poses a significant challenge, as the majority of patients (up to 58%) experience moderate to severe pain on the first post-operative day (*29*).

Although numbers of options are available for pain control after TKA, a standard pathway has not

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been established so far. The techniques that have been used traditionally for pain control include peripheral nerve blocks, epidural analgesia, parenteral (intravenous) analgesia (e.g., patient controlled analgesia) etc. But these techniques have shortcomings like inadequate pain control and unwanted side effects (*18,20,22*). Recently, the use of multimodal analgesia has been tried for postoperative pain relief. It is suggested that the use of local periarticular injections or local infiltration analgesia (LIA) may provide adequate analgesia, while limiting the use of parenteral opioids (and its side effects). LIA works on the principle of using multiple agents that have effect at different sites of the pain pathway. It not only controls pain adequately but also lowers overall opioid consumption, reduces length of stay (LOS) in the hospital, improves function and reduces the side effects of analgesics (*12,21,22*). In the present study we used a combination of local analgesic solution consisting of an opioid (Morphine), a non-steroidal anti-inflammatory drug (Ketorolac), a long-acting local anesthetic (Bupivacaine), and an antibiotic (Gentamycin), with Adrenaline, to determine the overall effect of this periarticular LIA on acute postoperative pain, joint function and length of hospital stay after primary TKA.

MATERIALS AND METHODS

After institutional ethics committee (IEC) approval (IEC review number - 227-20120-121-103498) and informed written consent, 100 consecutive patients who met the clinical and radiological criteria for unilateral primary TKA with American society of anaesthesiologists (ASA) physical status I to III and who were willing to provide informed consent were enrolled for the study. Patients with history of allergy to any of the study drugs, drug abuse, uncontrolled hypertension, history of stroke or a major neurological deficit, uncontrolled angina or chronic medical illness were excluded from the study. In addition patients with severe deformity (> than 20° varus and flexioncontractures) and restricted range of motion (< 90°) were excluded (to avoid implications related to postoperative assessment of range of motion). During the course of the study, 20 patients were excluded from the study for not meeting the required criteria (Fig. 1). Thus, 80 patients completed the criteria for this randomized double-blind controlled study (RCT).

Randomization and blinding

A random number table was utilized to generate the simple randomization sequence. Participants were randomly assigned to the two treatment groups : (1) Intervention group and (2) Control group. A randomization table was created with SPSS 10.04 software (SPSS, Chicago, Illinois). Forty patients (Fig. 1) were assigned to Intervention group (to receive an intraoperative periarticular injection of analgesic drugs) and forty patients were assigned to the control group (to receive normal saline injection). To ensure blinding, the local infiltration and control solution (both colourless) were prepared and provided in identical disposable syringes tagged with number codes for allocation concealment and blinding by an independent hospital pharmacist. The whole team concerned with postoperative care of the patients was blinded.

Anaesthesia and surgical procedure

The anesthesia regimen was standardized. No long-acting analgesics were used. All the patients received spinal anaesthesia with 3 mL of 0.5% Bupivacaine heavy with preservative free fentanyl 25 micrograms. Spinal anaesthesia was not possible in one patient in each group, and both patients were excluded from the study. No epidural anaesthesia was used in any of our patients during the study. The operation was performed by a single surgeon (first author) by a standard technique in both the groups. All operations were performed using anterior midline (Modified Insall's) approach (*25*), and a cemented posterior stabilised total knee system (Scorpio®, Stryker® Howmedica Osteonics ; Mahwah, NJ, USA) was used.

Pain management

Group A (intervention group) : In group A, local infiltration injection of a mixture ('cocktail') of drugs was given (Table I), using 20G hypodermic needle.

The first 20 mL was injected before implantation of components, into the periarticular soft tissues posteromedially and laterally in flexed position (Fig. 2). Special care was taken to avoid infiltration of the common peroneal nerve and popliteal fossa to avoid injury to vessels and sciatic nerve. Then, while the cement was curing, the quadriceps mechanism and the retinacular tissues were infiltrated with an additional 20 mL of the mixture. Finally, before wound closure, the subcutaneous tissues were infiltrated with remaining 35 ml solution (Fig. 3).

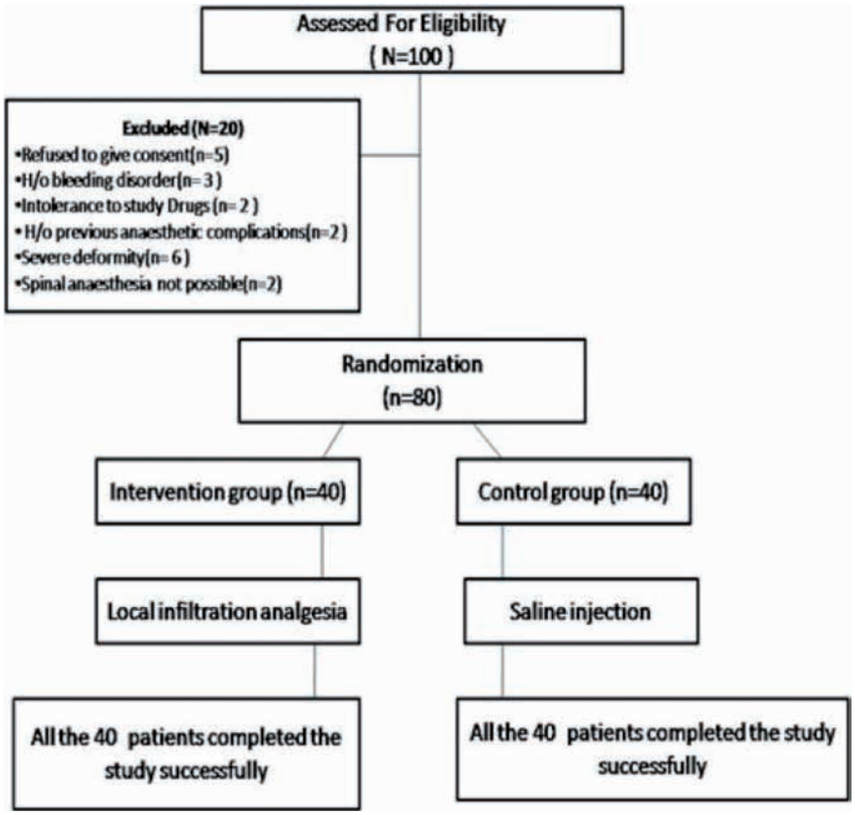

Fig. 1. — Events during the study

Table I. — Composition of 'Cocktail'

S. No.	Drug	Dose (conc.)	Volume (ml)
1.	Bupivacaine	0.25%	20
2.	Morphine	15 mg	1
3.	Ketorolac	30 mg	1
4.	Adrenaline	1 mg (1:1000)	1
5.	Gentamycin	80 mg	2
6.	Normal Saline	0.9%	50
	Total cost Rs 152 (< 3$)		75 ml Total

Group B (Control group) : In the control group same amount of saline injections was given intraoperatively.

Both the groups received

1. Patient Controlled Analgesia (PCA) morphine pump, which was used as rescue medication.
2. Injection Amoxicillin-clavulanate 1.2 g i.v. three times a day.
3. Injection Paracetamol 1 g i.v. three times a day.
4. Injection Diclofenac 75 mg i.v. two times a day.
5. Injection Enoxparin 0.4 ml subcutaneously once a day.

Patients were allowed to become mobile as tolerated beginning on the day of surgery under the supervision of physiotherapist.

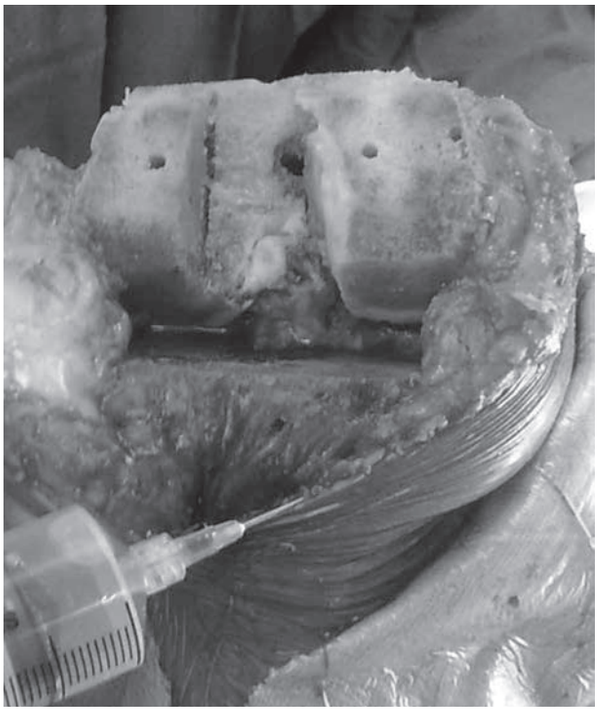

Fig. 2. — Intraoperative photograph showing the locations for deep intraoperative injection : posterior capsule (1) ; postero-medial structures (2) ; periarticular synovium (3).

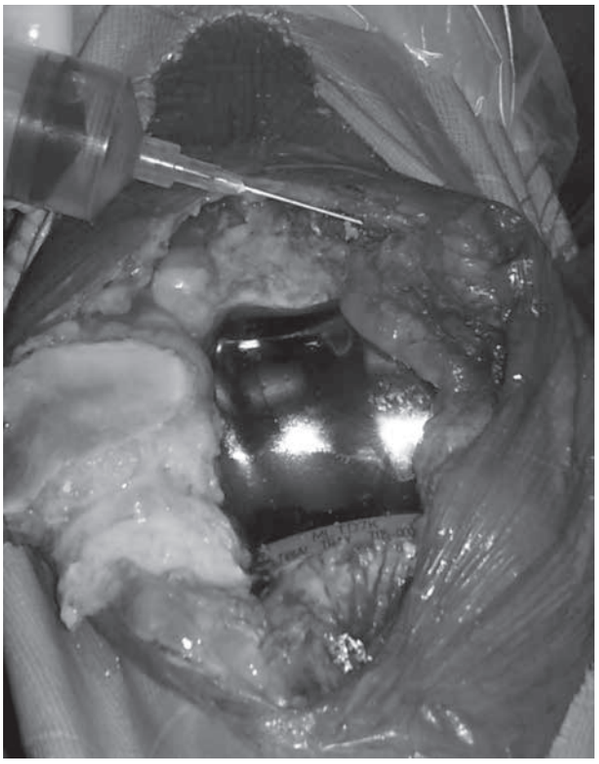

Fig. 3. — Intraoperative photograph showing the locations for superficial intraoperative injection.

Outcome measures

Participants were followed-up for 4-7 days after surgery. Assessment was conducted post-operatively, daily during the hospital stay.

Primary outcome measure

Post operative pain

Quality of analgesia was estimated by using Visual Analogue Score (VAS) of 0 to 10 at 6 h, 24 h, 48 h and 72 hours after surgery during rest and movement. The total amount of morphine (opioid) consumed was recorded by means of PCA pump over the first seventy-two hpurs after the surgery. All patients received PCA (a morphine bolus of 1.5 mg, a lock-out of six minutes, and a maximum of 15 mg/hr) for seventy two hours after the surgery. The consumption of PCA was measured at 0-6 hrs, 6-24 hrs and 24-72 hrs postoperatively and along with the patients' overall opioid consumption.

Secondary outcome measures

Satisfaction with in-patient pain relief : At the time of discharge, participants completed a 10 mm VAS to indicate their overall pain relief and compared in the two groups.

Length of hospital stay : This was calculated from participant's date of admission and discharge. The time to discharge was decided using the following criteria (4) :

- mild pain (VAS < 3) controlled by oral analgesics
- able to walk with support
- able to eat and drink, and
- no surgical complications.

Range of Motion : This was assessed by measuring postoperative knee flexion with a goniometer by the physiotherapist. The first attempt at mobilization was made 6 hrs postoperatively, when the patient was encouraged to stand up and walk 2-3 steps. If unsuccessful, mobilization was attempted again on the following day. Patients were discharged when they fulfilled the discharge

criteria. The physiotherapist recorded the ability to flex the knee on 3rd postoperative day.

STATISTICAL ANALYSIS

The data was revealed to the investigators at the end of the study. The statistical analysis of the data set was performed with Kolmogorov-Smirnov test ($p < 0.05$) for normality and an unpaired-t test was used to compare mean of the group for the significance of differences of outcome variable. Dichotomous data were analyzed using chi-square test or Fisher's exact test, as appropriate. A p-value of < 0.05 was considered statistically significant. A power analysis to determine the study groups was performed. For the significance level (alpha) at 5% and the power (1-beta) of study at 80%, a minimum of 40 samples (calculation based on similar previous studies) were required per group to detect a difference in mean value of pain and length of stay in the two groups of patients using the unpaired t-test. Assuming 20% of dropouts during the trial, we decided to take a sample size of a total 100 patients.

RESULTS

Among the 100 consecutive unilateral primary TKA patients between May 2012 and December 2012, the 80 consenting and eligible patients were recruited and all the recruited patients completed the trial (Fig. 1).

Demographic data

Demographic variables were comparable for the two groups (Table II).

Pain relief

VAS at rest

Mean VAS pain score at rest was lower in intervention group than in control group ($p < 0.001$) at 6 hrs, 24 hrs,48 hrs and 72 hrs (Fig. 4).

VAS with movement

With movement VAS pain scores were lower in intervention group than in control group at 6, 24, and 48 hrs ($p < 0.001$) and at 72 h ($p = 0.001$) (Fig. 5).

The local analgesia group had a significantly lower mean VAS for pain during exercise than did the control group (3.5 compared with 4.32) on the first postoperative day ($p < 0.0001$, Fig. 10) as well as a significantly lower VAS at rest ($p = 0.0001$, Fig. 4) .

Table II. — Demographic and perioperative data

Variables	Intervention group	Control group	P value	Result
Demographic				
Age (years)**	64.13 ± 1.14	64.68 ± 9.33	0.768	NS
Gender				
Male*	08	13		
Female*	32	27		
(M:F)	8:32 (20%:80%)	13:27 (32.5%:67.5%)	0.2039	NS
Side involved				
Right*	21	24		
Left*	19	16		
BMI (kg/m^2)	27.12 ± 2.78	26.88 ± 1.96		NS
Tourniquet time**	41.47 ± 5.64	42.25 ± 6.40		NS

* The values are given as the no. of patients. ** The values are given as mean and standard deviation ; NS : not significant.

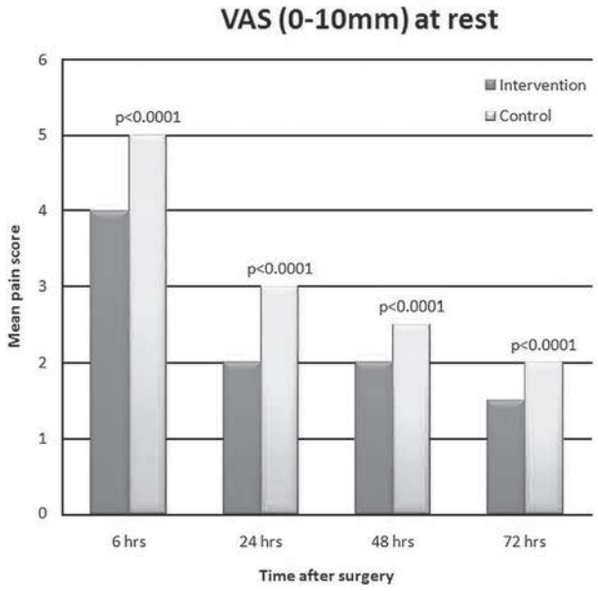

Fig. 4. — Mean VAS score at rest

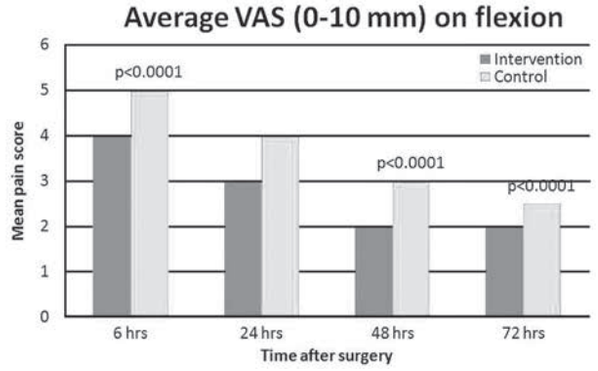

Fig. 5. — Mean VAS score on movement

Opoid Consumption

The total mean morphine consumption was significantly lower in intervention group during first seventy two hours postoperatively compared to control group (Fig. 6). There was significant difference in opioid consumption in first 6 hrs compared to 6-72 hrs period.

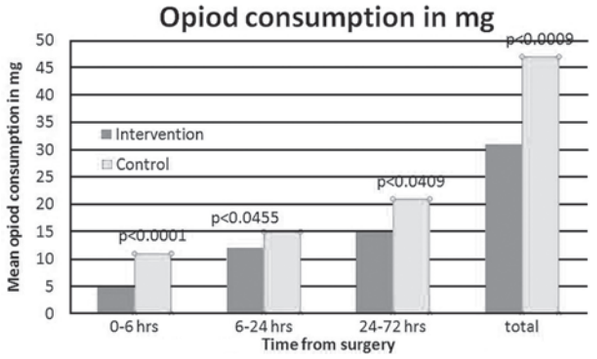

Fig. 6. — Mean opioid consumption

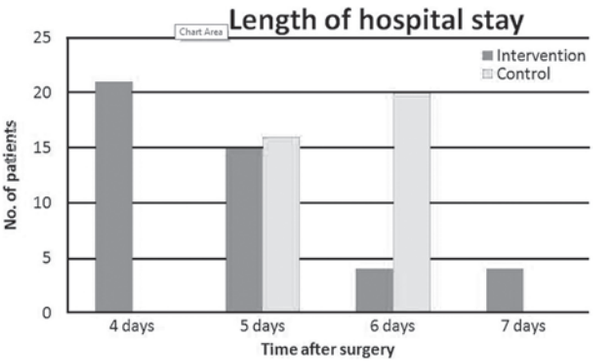

Fig. 7. — Duration of hospital stay.

Secondary end points

Hospital stay

The average LOS was significantly lower ($p < 0.0001$) in intervention group compared to control group (Table III). In the intervention group, 21/40 patients were discharged during the fourth postoperative day, 15/40 on 5th postoperative day and 4 on 6th postoperative day as compared to 16/40 on 5th postoperative day, 20 on 6th and 4 on 7th post-operative day in the control group (Fig. 7).

Range of motion

Postoperative knee flexion on 3rd postoperative day was improved in the infiltration group (Fig. 8 and 9). The mean range of motion in the infiltration group was 90° as compared to 59° in the control group, 72 hours post-operatively ($p < 0.00001$).

Table III. — Length of Stay in the intervention and control group

	Mean length of stay		
	Intervention group	Control group	p value
Hospital stay	4.5 ± 0.67	5.7 ± 0.64	< 0.0001

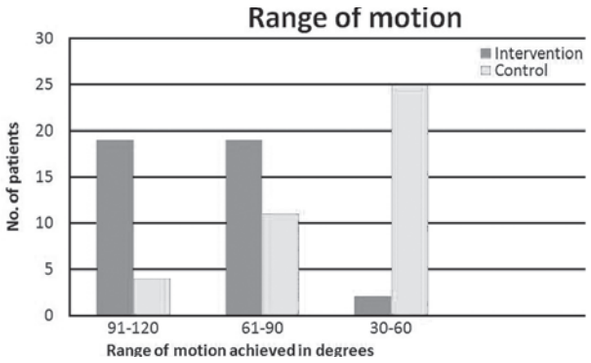

Fig. 8. — Range of motion on 3rd post operative day

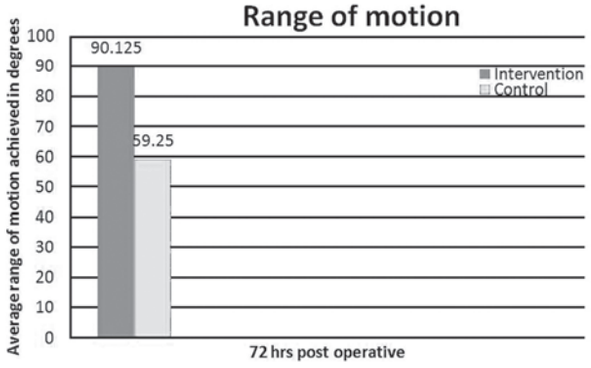

Fig. 9. — Mean range of motion on 3rd postoperative day

Patient Satisfaction with pain

There was significant difference for patient satisfaction with pain between the two groups at 72 h (Fig. 10). The mean VAS score in intervention group was lower (2.3) as compared to the control group (3.4).

Complications

No serious complications directly attributable to LIA technique were recorded postoperatively. In particular, we observed no major toxicity involving cardiac arrest, cardio toxicity (including widening of the Q-T interval and QRS complex in the ECG). We also observed no wound infection during the study. Minor adverse events noted included transient mild to moderate nausea, vomiting, and dizziness – usually associated with postural hypotension on the first attempt to walk at about 4-5 h postoperatively or with the use of supplementary morphine. Evaluation of complications revealed that in intervention group : 3 patients had nausea, 1 patient had dizziness, 1 patient had vomiting and 1 patient had tachycardia. Control group : 5 patients had nausea, 2 patients had dizziness and 1 patient had urinary retention.

Fig. 10. — Patient satisfaction with pain

DISCUSSION

TKA is associated with significant pain that is severe in approximately 60% of patients and moderate in approximately 30% of patients (*4*). The cause of pain is multi factorial and may arise as a result of trauma to the bone or surrounding tissues during surgery or due to hyper-perfusion following tourniquet release (*10*). Surgical trauma during TKA modifies the responsiveness of the nervous system in two ways. It causes "peripheral sensitization" and increases the response to noxious stimuli and decreases the pain threshold at the site of the injured tissue as well as uninjured tissue and it causes

"central sensitization" by increasing the excitability of spinal neurons (*28*), together these changes contribute to postoperative pain. The optimal form of pain relief is one that is applied preoperatively, perioperatively, and postoperatively to avoid the establishment of pain hypersensitivity (*2*) and allows effective postoperative rehabilitation and a good overall outcome (*24*).

Although many analgesia protocols for TKA have been evaluated, none is optimal and narcotics still play a major role in post operative pain relief (*1,23,27*). Epidural infiltration although effective but may be associated with side effects (e.g. nausea, pruritus, urinary retention, hypotension, poor muscle control, and delayed mobilization) (*7,11*) and moreover, the risk of epidural hematoma with concomitant thromboprophylaxis is still a major concern (*13*). It also requires specialised monitoring. Nerve blocks do reduce the occurrence of side effects and complications related to epidural or self-administered analgesia (*8*), however, to effectively control pain, it may be necessary to block multiple nerves like the femoral, sciatic and obturator nerves ; besides the danger of injuring the nerves (*19*). Nerve blocks are technically difficult procedures, requiring additional equipments, operative time and can only be performed by an experienced anaesthetist.

Multimodal local infiltration analgesia (LIA) technique involves infiltration of a large volume of diluted solution of a long-acting local anaesthetic agent (Bupivacaine or Ropivacaine), often with adjuvants (e.g. Epinephrine, Ketorolac, an opioid) in the soft tissues during surgery. All the adjuvants which are used have different modes of action on the pain pathway and hence their effect is multimodal. This technique was first introduced by Kerr et al (14), specifically to avoid sedation and facilitate rapid physiological recovery after lower limb arthroplasty to enable early mobilization and discharge. LIA into periarticular soft tissues following TKA has shown to provide pain relief while permitting accelerated rehabilitation besides reducing requirements for postoperative analgesia and allowing reduction in hospital stay (*6,16*).

This study was specifically designed to investigate the efficacy of LIA on postoperative pain management following TKA. Secondarily, its effect on range of motion, length of hospital stay and overall patient satisfaction with pain was also noted. The active ingredients of the infiltration mixture that were used in the present study were Bupivacaine, Ketorolac, Morphine, Adrenaline and Gentamycin administered intraoperatively. In some studies maximum permissible limit of 80 ml of Bupivacaine has been used in one knee (*17*) while in this study only 20 ml of the same drug was used to avoid possible toxicity of Bupivacaine. Instead NSAID (Ketorolac) was used to enhance the analgesic and anti-inflammatory effect of the 'cocktail'. Non-steroidal anti-inflammatory drugs (NSAIDs) – mostly Ketorolac 30 mg (*14*) which is a directly acting injectable formulation and Morphine (*21*) have been used, in addition to Epinephrine. Steroid (methylprednisolone) has also been used in the infiltration mixture (*21*) but it was avoided in this study to avoid the possibility of increased risk of infection.

The study revealed significant pain relief with the use of intraoperative infiltration, during the initial postoperative period (Fig. 4 and 5) in the intervention group at 6 hrs, 24 hrs and 72 hrs ; which was consistent with other published studies (*3,16,17*) and possibly, it also resulted in an increased range of knee motion (Fig. 8 and 9) and early discharge from the hospital (Fig. 7). Bupivacaine, at higher doses, can induce arrhythmias, which can be dangerous. In this study only 50 mg (20ml) of Bupivacaine along with 30 mg of Ketorolac was used to achieve the same analgesic effect.

The capacity of LIA to achieve adequate pain relief and allow early mobilization without prolonging recovery or LOS was also assessed. Since several factors can affect duration of hospital stay, an objective method to assess the criteria for discharge was used. These criteria have been used by other authors as a way of objectively assessing recovery and discharge (*21*). Significant difference was noted in the average LOS ($p < 0.0001$) along with significantly greater mean VAS for patient satisfaction ($p = 0.0001$) (Fig. 10). Lamplot *et al* (*16*), also showed decreased hospital stay in the multimodal group as compared to the PCA group. However, Lombardi *et al* (*17*) did not find any significant difference in LOS and ROM despite

claiming good pain relief after LIA. Adequate pain control in immediate postoperative period is one of the main contributory factors in reducing LOS. The results of this study have shown that there was a substantial reduction in duration of hospital stay without having a negative effect on patient satisfaction, which are similar to other published reports (*3,26*).

In addition to adequate pain relief, the total consumption of opioid analgesics was lower in the LIA group than in the control group (Fig. 9), during the 72 hrs test period ($p < .0001$), which in turn resulted in a lower incidence of opioid-related side effects (including sedation, pruritus, and nausea) when LIA was used compared to control group, where only saline was used.

Only minimal and non serious complications were noted in the present study. In infiltration group, only 3 patients had nausea and 1 patient had vomiting which may be related to morphine use. Only 1 patient had tachycardia which was temporary and fully reversible. This was correlated to the use of adrenaline. Although many published studies have used Ropivacaine in their infiltration mixture (less cardiotoxic etc) but no complication directly related to Bupivacaine was noted in the present study.

In other published studies (*16*) the control group either had no infiltration or was managed with parenteral Morphine. Hence there was an apparent bias in these studies, as the user (surgeon) already knew which patient is having LIA. But in the present study, since both the groups had similar looking infiltration of LIA or saline this bias was avoided.

Browne *et al* (*5*) in 60 TKAs used intra-articular Bupivacaine along with epinephrine and reported a decreased time to discharge in the infiltration group although the decrease in pain levels in their study was not statistically significant. Krenzel *et al* (*15*) in a randomised double blind study comparing local Ropivacaine infiltration with placebo along with femoral nerve block, found out that there was a decrease in the pain score in the early post operative period but did not discuss the impact on discharge from the hospital.

However, there were some limitations to the present study. A comparatively larger sample size could have helped in further reducing the bias. Due to the mixture of multiple agents used in the multimodal analgesia in the test group, it is difficult to ascertain the efficacy of any one particular drug.

Pain is not only an unpleasant feeling for the patient but its control can be quite difficult and expensive as it involves the use of various drugs, treatment of side effects related to the use of pain relieving medication, additional manpower, excessive length of stay in hospital etc. Hence, it is essential to use a protocol which can address all these issues. LIA mixture used in the present study was highly cost effective as it only costs < $ 3 and moreover it reduced the requirement of other pain killers which further reduced the hospital cost to the patient. None of the published studies so far have studied the cost effectiveness of LIA in the post operative pain relief of patients undergoing total knee arthroplasty.

CONCLUSIONS

LIA technique with multimodal drugs after TKA can significantly improve pain control both during rest and on movement and hence obtain higher patient satisfaction. It can significantly reduce the requirements for morphine with patient-controlled analgesia (PCA) and opioid related side effects. LIA allows improved range of motion and early discharge from the hospital and therefore is cost effective.

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