ORIGINAL ARTICLE

Effect of periarticular clonidine on postoperative pain and function after total knee arthroplasty

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ABSTRACT

Introduction: Various modalities are available for perioperative pain management in total knee arthroplasty (TKA) including periarticular infiltration of an "analgesic cocktail". The purpose of this study was to investigate the effect of periarticular injection with clonidine on postoperative pain scores and functional recovery following TKA.

Materials and Methods: In this prospective randomized controlled study involving 150 consecutive TKAs (104 patients), patients were allotted to 3 groups consisting of control group A (no periarticular infiltration), group B (infiltration without clonidine) and group C (infiltration with clonidine). All the 3 groups were compared in terms of pain, length of hospital stay and rehabilitative milestones during the immediate postoperative period.

Results: In group A, length of hospital stay, mean visual analogue pain scores, straight leg raising and extensor lag at the time of discharge and time for stick ambulation after surgery was significantly different compared to the other two groups whereas it was no different when group B and group C were compared.

Conclusion: Addition of clonidine to the periarticular injection provided no significant additional benefit in terms of postoperative pain and functional recovery following TKA.

Keywords: total knee arthroplasty; periarticular infiltration; clonidine; analgesia

INTRODUCTION

Severe pain after total knee arthroplasty (TKA) is common and adequate pain management is often challenging. Severe postoperative pain may lead to prolonged hospital stay, delayed commencement of physiotherapy and delayed functional recovery, poor patient satisfaction, and increased consumption of analgesics and higher risk of associated complications. Various modalities are available for perioperative pain management in TKA, ranging from regional anaesthesia, periarticular analgesic infiltration, and oral and parenteral opiates and non-steroidal anti-inflammatory drugs. Several reports have highlighted the efficacy of multimodal pain management approach using a combination of these methods in TKA [4, 9, 15, 17, 18, 23].

Providing local analgesia by periarticular infiltration of an "analgesic cocktail" has been reported to be very effective in postoperative pain management after TKA [2, 3, 6, 8, 12-14, 20, 21]. This takes advantage of the additive effect of various analgesics which act locally through different pathways, thereby allowing the use of smaller doses of oral or parenteral analgesics postoperatively and consequently diminishing the potential for complications caused by them [11, 15, and 23]. Agents commonly used intra-articularly for postoperative pain control include morphine, bupivacaine, methylprednisolone, neostigmine, epinephrine, ketorolac and clonidine.

Clonidine, an alpha-2 adrenergic agonist, when combined with other agents has been reported to provide significant improvement in analgesia when used in patients undergoing knee arthroscopy [1, 7, 22]. However, we did not find any reports in literature which investigated the efficacy of periarticular clonidine infiltration in patients undergoing TKA. The aim of this prospective randomized controlled trial was to investigate the effect of periarticular injection with clonidine on postoperative pain scores and functional recovery following TKA. We hypothesized that the addition of clonidine in the periarticular injection will improve postoperative pain scores and functional recovery following TKA when compared to periarticular injections without clonidine.

MATERIALS AND METHODS

All patients scheduled for primary TKA for knee arthritis at our hospital over a 6-month period between July 2007 and December 2007 were assessed for eligibility for enrollment into the study. A study protocol was devised and an approval from the hospital's Ethics Committee was obtained. Based on the recommendations of the CONSORT statement for prospective randomized controlled study (http://www.consort-

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statement.org), a study strategy was constructed. The aim of the study was to establish any difference in the pain and functional outcome in 3 groups consisting of a control group A (knees with no periarticular injection), group B (knees with periarticular injection without clonidine) and group C (knees with periarticular injection with clonidine).

Based on the results of a previous study [8], power calculation indicated that a sample size of 48 knees were needed in each group to show a significant difference (alpha=0.05, power=0.8). Block randomization was used to assign patients to one of three groups. Consecutive patients who were to undergo TKA were randomly assigned to a particular day of the week for surgery during preoperative assessment in the outpatient department by the operating surgeon. Based on which day of the week they were assigned, a particular regimen of anaesthesia and postoperative pain management protocol was followed. Patients operated on Tuesdays and Thursdays were in group A, Wednesdays and Saturdays were in group B and Mondays and Fridays were in group C. The inclusion criteria consisted of primary total knee arthroplasties, primary osteoarthritis, and ability to give informed consent. Exclusion criteria included rheumatoid arthritis, allergies to any of the ingredients of the injection, known drug dependencies, major psychological problems, and for the clonidine group, patients with cardiovascular disorders on beta-adrenergic blockers. All patients were blinded to the use of periarticular injection.

All TKAs were performed by a single surgeon (AM) using the computer-assisted technique. All procedures were performed with the tourniquet inflated, which was deflated after the cement had hardened. An anterior longitudinal incision and a medial parapatellar arthrotomy were used. All patients underwent TKA using a cemented, posterior cruciate substituting design (P.F.C Sigma, DePuy Orthopaedics, Warsaw, Indiana) and all patients had resurfacing of the patella. We used the Ci navigation system with its software (BrainLab, Munich, Germany). Conventional cutting blocks were navigated into position to perform the appropriate bone cuts. The degree of soft tissue release was governed by the amount of soft tissue tightness assessed using a tensioning device and medial and lateral gap imbalance as quantified by the computer. Medial release for varus knees and lateral release for valgus knees were performed to achieve rectangular balanced gaps and a fully restored mechanical axis.

The type of anaesthesia and postoperative pain control protocol in each group is summarized in Table 1. All patients in group A received a combined spinal and epidural anaesthesia and patients in group B and C received either general or regional anesthesia. All patients in group B and group C received a periarticular analgesic cocktail infiltration during the procedure when the cement was curing and before the tourniquet was deflated. The cocktail in group B (periarticular injection without clonidine) contained 0.5% Bupivacaine (2.5 mg/ kg), Fentanyl 150-200 mcg and Cefuroxime 750 mg which were diluted with 0.9% normal saline to a total volume of 50 ml. In group C (periarticular injection with clonidine), in addition to the above constituents, Clonidine (1 mcg/ kg) was added. The analgesic cocktail was prepared by the anaesthetist under strict aseptic precautions and surgeon was blinded to the addition of clonidine to the cocktail. The structures that were infiltrated included the edges of the arthrotomy, medial collateral ligament, retropatellar fat pad, and posteromedial soft-tissue sleeve. The arthrotomy was closed over a negative suction drain and a compression dressing was applied.

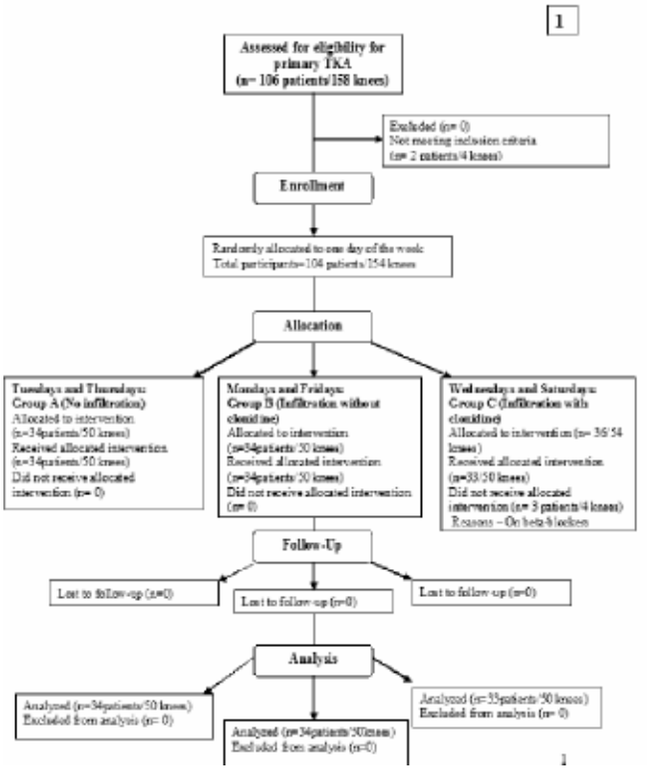
Postoperatively, patients in Group A received continuous

Table 1: Summary of the type of anaesthesia and postoperative pain management protocol in each group

Group A (knees with no periarticular injection)
Anaesthesia: Spinal + Epidural
First 24 hours postoperatively: Epidural pump (bupivacaine 3.6mg/ml @ 2-4 ml/hr)
Next 48 hours postoperatively: Intravenous Tramadol 50 mg 8th hourly + Tablet Paracetamol 650 mg 8th hourly + Diclofenac suppository 12.5 mg at night + local ice fomentation 4-5 times/day
After 72 hours postoperatively till discharge: Tablet Paracetamol 650 mg 8th hourly + Diclofenac suppository 12.5 mg at night + local ice fomentation 4-5 times/day + Intravenous Tramadol 50 mg as and when needed
Group B (knees with periarticular injection without clonidine)
Anaesthesia: Regional (Spinal or Epidural) or General
Intraoperative periarticular injection: 0.5% Bupivacaine (2.5 mg/ kg) + Fentanyl 150-200 mcg + Cefuroxime 750 mg diluted with 0.9% normal saline to a total volume of 50 ml
First 48 hours postoperatively: Intravenous pump (200 mg Tramadol + 20 mg Ondansetron)
After 48 hours postoperatively till discharge: Tablet Paracetamol 650 mg 8th hourly + Diclofenac suppository 12.5 mg at night + local ice fomentation 4-5 times/day + Intravenous Tramadol 50 mg as and when needed
Group C (knees with periarticular injection with clonidine)
Anaesthesia: Regional (Spinal or Epidural) or General
Intraoperative periarticular injection: 0.5% Bupivacaine (2.5 mg/ kg) + Fentanyl 150-200 mcg + Cefuroxime 750 mg + Clonidine (1 mcg/ kg) diluted with 0.9% normal saline to a total volume of 50 ml
First 48 hours postoperatively: Intravenous pump (200 mg Tramadol + 20 mg Ondansetron)
After 48 hours postoperatively till discharge: Tablet Paracetamol 650 mg 8th hourly + Diclofenac suppository 12.5 mg at night + local ice fomentation 4-5 times/day + Intravenous Tramadol 50 mg as and when needed

Figure Legends

Figure 1: Participant flow diagram showing enrollment and randomization



epidural infusion (bupivacaine 3.6 mg/ml at the rate of 2-4 ml per hour) for first 24 hours after the procedure followed by intravenous analgesics (intravenous tramadol 50 mg, 8th hourly) for the next 72 hours. All patients in group A were put on an indwelling Foley's urinary catheter in view of the epidural pump which was removed over the next 48 hours. Thereafter the patient was shifted to oral analgesics (tablet tramadol 37.5mg+ acetaminophen 325 mg 8th hourly) and diclofenac suppository 12.5mg at night till discharge. In case the pain remained intolerable after shifting to oral analgesics, intravenous tramadol 50 mg was administered as and when required depending on the severity of pain. All patients in group B and C received an intravenous analgesic pump (containing 200 mg Tramadol + 20 mg Ondansetron) for the first 48 hours. Thereafter the patient was shifted to oral analgesics and occasional intravenous tramadol as described above till discharge. For thromboprophylaxis, a sequential compression device was applied for the first 24-36 hours and a daily dose of 3200 IU of low molecular weight heparin (LMWH) was administered subcutaneously till discharge. After discharge, all patients were given either tablet aspirin or clopidogrel 75 mg twice daily for a total of 3 months after surgery. Pre and postoperative pain was scored by the patient using a Visual Analogue Scale (VAS) consisting of a 10-cm line with absence of pain at one end (0) and the most extreme pain they have ever felt at the other end [10] of the line. Pain scores were recorded preoperatively and everyday postoperatively until discharge.

All patients were made to perform bedside range of motion exercise, static quadriceps exercise, and ambulate using a walking frame on the first postoperative day. The exercises were increased as per patients comfort level to achieve maximum flexion and extension of the knee, sitting on a chair, and independent ambulation using a walker or a stick. Functional recovery was monitored in all patients by noting the ability to perform active straight leg raising (SLR), degree of flexion and the amount of extensor lag in the sitting position as measured by a goniometer. Faradic stimulation of quadriceps was considered if the patient had an extensor lag of ≥30° on the 3rd postoperative day despite the above-described physiotherapy regime. Patients were allowed to use a walking stick when the extensor lag was ≤10° and they were able to walk full weight bearing in a stable fashion. A patient was considered due for discharge if walking independently with a walker or a stick, and able to sit in a chair. The time taken for the patient to walk independently using a walker and a walking stick (wherever possible) was noted and functional recovery was recorded on each day postoperatively until the patient was discharge. Patients were observed for side-effects of giddiness, hypotension, bradycardia, vomiting, low urinary output, urinary retention, sedation, and other complications which the patient developed during their hospital stay were also noted.

Participant flow diagram showing enrollment and randomization is detailed in Fig. 1. All patients were evaluated pre and postoperatively using the Knee Society Score and body mass index (BMI) was determined. Standing full length (hip to ankle) weight-bearing radiographs, weight-bearing anteroposterior knee radiographs and knee lateral radiographs were obtained in all patients pre and postoperatively. The degree of knee deformity or hip-knee-ankle (HKA) angle was determined on the standing full-length radiographs as the angle between the mechanical axis of the femur (centre of the femoral head to the centre of the knee joint) and the mechanical axis of the tibia (centre of the knee joint to the centre of the ankle). All data was recorded by an orthopedic fellow unaware of the objective of the study as part of routine postoperative patient assessment.

Statistical analysis was performed using SPSS version 14 statistical software (SPSS, Chicago, Ill). Data was analysed using analysis of variance. When a significant result was obtained, a post-hoc analyses was made using Dunnett T3 test for multiple comparisons. Categorical data was compared between the groups using the Fisher's exact test. Statistical significance was defined as $p<0.05$.

RESULTS

Preoperative patient characteristics are summarized in Table. 2. There were 34 patients in group A and B (50 knees, 16 bilateral and 18 unilateral each) and 33 patients in group C

Table 2: Preoperative parameters in all 3 groups

Parameters	**Group A** (no periarticular injection)	**Group B** (periarticular injection without clonidine)	**Group C** (periarticular injection with clonidine)
Number (knees)	50	50	50
Age (years)	66.6±6.5 (54-79)	69.1±8.1 (53-94)	67.4±7.0 (55-83)
BMI	28.6±5.3 (21.8-53.8)	31.2±4.8 (24-40.7)	29.1±3.8 (23.7-42)
Preoperative knee deformity (degrees)	166.8±5.6 (150-174)	168.8±5.5 (155-180)	168.0±7.1 (150-192)
Preoperative Knee Score	49.2±9.5 (24-80)	48.3±12 (28-79)	49.4±12.3 (18-77)
Preoperative Function Score	47.7±7.7 (20-60)	46.5±13.9 (10-80)	48.4±6.7 (20-60)
Preoperative VAS Score	5.6±2.0 (0.9-10)	5.5±2.3 (1.2-10)	6.4±2.1 (3-10)

BMI – body mass index; VAS – visual analogue scale (0=No pain, 10=Maximum pain)
All values are given as mean±standard deviation (range)

(50 knees, 17 bilateral and 16 unilateral). Preoperatively the 3 groups were similar with respect to age, preoperative deformity, preoperative knee and function score and preoperative VAS score. The mean BMI differed significantly between group A and group B (p=0.01) whereas there was no significant difference between group B and group C and between group A and group C. Postoperative parameters in each group is summarized in Table 3. While groups B and group C differed significantly in terms of VAS score at discharge, amount of extensor lag and straight leg raising at discharge, length of hospital stay and the time for stick walking when compared to the control group A, the difference was not statistically significant when group B and C were compared (Table 4). There was no significant difference between the groups for knee range of motion at discharge and time for ambulation with a walker.

Three patients in group A had urinary retention after removal of Foley's catheter which required draining with a catheter, 5 patients had complaints of nausea and vomiting during the first 72 hours which settled with anti-emetics, 4 patients had low urinary output on day 3 which resolved with medical management and 6 patients had giddiness on postoperative day 1 which resolved gradually over the next 24 hours. In group B, 2 patients had low urinary output on day 3 which resolved with medical management, 3 patients had nausea and vomiting during the first 72 hours which settled with anti-emetics and 4 patients had giddiness on postoperative day 1 which resolved gradually over the next 24 hours. In group C, 3 patients had low urinary output on day 3 which resolved with medical management, 2 patients had nausea and vomiting during the first 72 hours which settled with anti-emetics and 3 patients had giddiness on postoperative day 1 which resolved gradually over the next 24 hours. In addition,

Table 3: Postoperative parameters in all 3 groups

Parameters	**Group A** (no periarticular injection)	**Group B** (periarticular injection without clonidine)	**Group C** (periarticular injection with clonidine)
Length of hospital stay (days)	5.7±1.6 (4-10)	4.8±1.2 (2.5-8)	4.8±1.0 (3-7)
VAS Score at discharge	4.6±1.3 (2-7.2)	3.2±2.1 (0.5-9)	2.9±1.6 (0-6)
Knee ROM at discharge (degrees)	97.8±8.6 (80-110)	97.9±9.0 (80-115)	98.1±6.7 (90-110)
Extensor lag at discharge (degrees)	10.5±7.7 (0-30)	2.8±5.3 (0-20)	1.1±3.8 (0-20)
Straight leg raising positive at discharge	26% (13/50 knees)	66% (33/50 knees)	80% (40/50 knees)
Time for walker ambulation (hours postoperatively)	43.2±16.0 (24-72)	40.3±14.0 (24-72)	42.2±16.4 (24-72)
Time for stick ambulation (hours postoperatively)	109.5±23.8 (72-168)	73.6±16.4 (42-120)	70.4±27.1 (24-144)

VAS – visual analogue scale (0=No pain, 10=Maximum pain); ROM – knee range of motion.
All values are given as mean±standard deviation (range).

Table 4: Comparison of postoperative parameters between the 3 groups

Parameters	Group A versus Group B	Group B versus Group C	Group A versus Group C
Length of hospital stay	0.002	>0.05	0.003
VAS Score at discharge	<0.0001	>0.05	<0.0001
Knee ROM at discharge	>0.05	>0.05	>0.05
Extensor lag at discharge	<0.0001	0.44	<0.0001
Straight leg raising positive at discharge	0.0001	0.17	<0.0001
Time for walker ambulation	>0.05	>0.05	>0.05
Time for stick ambulation	<0.0001	>0.05	<0.0001

VAS – visual analogue scale; ROM – range of motion
p<0.05 is statistically significant
Group A (knees with no periarticular injection), Group B (knees with periarticular injection without clonidine) and Group C (knees with periarticular injection with clonidine)

one patient each had pneumonitis and intestinal pseudo-obstruction in group C, both of which resolved with medical management.

DISCUSSION

A common consensus among joint replacement surgeons is that postoperative pain after TKA should be managed aggressively in order to optimize surgical outcomes [16]. Multimodal pain control methods with periarticular injection have been an important advancement in perioperative pain care after TKA. Numerous studies have reported periarticular injection to be an important adjunct to the multimodal approach to controlling pain and improving function after total knee arthroplasty [2-4, 6, 8, 12-15, 20, 21, 23]. These studies have used numerous drugs in varied combination to show better efficacy when compared to other modalities like PCA, epidural infusion, femoral nerve block or placebo injections with normal saline. The typical contents of the periarticular infiltration cocktail as reported in many studies are usually bupivacaine plus epinephrine and keterolac or morphine. Few investigators have also similarly investigated the addition of a steroid like methylprednisolone or betamethasone in the periarticular injection cocktail [4, 6, 17].

In the current study, the mean postoperative VAS score was significantly lower in the injection groups (group B 3.2±2.1 and group C 2.9±1.6) compared to the control group A (4.6±1.3). Similarly the functional outcomes in terms of straight leg raising, extensor lag and stick walking were also significantly better in the injection groups compared to the control group. These results clearly confirmed the efficacy of periarticular injection containing a combination of bupivacaine and fentanyl in improving postoperative pain scores and functional outcomes similar to results previously reported in literature [2, 3, 6, 8, 13, 20].

Clonidine, an alpha-2 adrenergic agonist, has a long history of use in pain management and has been administered topically, orally, neuraxially and intra-articularly [19]. It has been tested extensively in knee arthroscopy as an adjuvant for pain management and has been reported to provide significant improvement in analgesia postoperatively when used intra-articularly [1, 7, and 22]. We could not find any studies in literature which have reported the effect of addition of clonidine in the periarticular injection used in TKA. However, the effect of addition of clonidine in epidural anaesthesia in patients undergoing TKA has been reported. Forster and Rosenberg 5 in a prospective, randomised, double blinded study reported that clonidine augmented analgesia after TKA when added to a continuous low-dose epidural infusion of ropivacaine and fentanyl. However, patients administered with clonidine had a significantly higher incidence of hypotension and bradycardia. Similarly, Huang et al [10] demonstrated that, when added to a lumbar epidural mixture of ropivacaine and morphine, 1.0 mcg/mL clonidine augmented analgesia after TKA surgery without significant adverse effects. The option of administration of clonidine with epidural infusion although effective in controlling pain may be associated with risks of prolonged sensory and motor blockade, bradycardia and hypotension which may delay rehabilitation after TKA [5, 10, 11.] Maheshwari et al [15] have advocated the administration of clonidine via transdermal patch. However, this route may be associated with side-effects and its efficacy has not been investigated.

The mechanism of peripheral action of clonidine is still unclear and investigators have proposed that it could be the result of blockage of peripheral nerve conduction, local release of enkephalin-like substance and stimulation of specific alpha-2-adrenergic receptors which inhibits noradrenergic release at nerve endings [19]. Clonidine has also been reported to have a synergistic effect on intra-articular bupivacaine and morphine and has opiate-sparing effect [1, 7.] However, the addition of clonidine in the periarticular injection in the current study of TKAs failed to show any advantages in terms of pain and functional outcome at the

time of discharge. Although the number of limbs with postoperative lag and absence of straight leg raising at the time of discharge was far greater in Group B compared to Group C, the difference was statistically not significant.

Clonidine has been reported to cause hypotension and bradycardia as a side-effect especially when used in epidural anaesthesia [5, 10]. In the current study, 16 patients in group A had 18 side-effects (47%) postoperatively compared to 8 patients with 9 side-effects (23.5%) in group B and 7 patients with 8 side-effects (21.2%) and 2 patients with 2 complications in group C. Although, the incidence of side-effects in the control group A was significantly greater compared to group B and group C ($p=0.03$, Fisher's exact test), the incidence of side-effects in group B was not significantly different when compared to when compared to group C ($p>0.05$, Fisher's exact test). This difference in the incidence of side-effects may have been due to the higher dose of intravenous tramadol given in group A (450 mg over 3 days) compared to group B and C (200 mg over 2 days). None of the patients in group C had any episode of bradycardia. However, 3 patients in this group had complaints of giddiness on day 1 when they were made to stand and transient fall in blood pressure was recorded during these episodes. However it resolved on its own gradually over the next 24 hours. Similarly 6 patients in group A and 4 patients in group B had episodes of giddiness and hypotension on day 1. These episodes in all the 3 groups were most probably due to postural hypotension which resolved on its own with increased duration of sitting up by the patients. In group A, this may also have been aggravated by the presence of epidural infusion maintained during the first 24 hours after surgery.

This study was not without limitations. Although patients in all 3 groups were administered a fixed dose of intravenous tramadol during the first 48-72 hours postoperatively (450 mg of tramadol or 50 mg 8th hourly per day over 72 hours in group A and 200mg tramadol through a pump over 48 hours in group B and C), data is not available on mean consumption of opiates or analgesics in each group. Hence the opiate-sparing effect of clonidine could not be investigated in the current study. The current study has recorded the pain and functional outcome in the 3 groups only till the time of discharge and hence no conclusions can be made regarding the pain and functional outcome after the patient has been discharged. Lastly, although the observer who recorded pain score and knee function and the patients themselves were blinded to the infiltration procedure, the study may be biased towards relief of pain with injection and ideally a placebo group (such as injection of saline alone for group A) should have been part of the study.

In conclusion, the results of this prospective, randomized, controlled study demonstrates excellent pain relief and functional recovery in patients who had periarticular infiltration during TKA when compared to patients managed with epidural infusion and intravenous analgesics. However, addition of clonidine in the periarticular injection does not improve postoperative pain scores and functional recovery following TKA when compared to periarticular injections without clonidine.

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