



Comparative Study between Adductor Canal Block, Femoral Nerve Block and Epidural Analgesia for Management of Post-Operative Pain in Total Knee Replacement

**Heba Salah Eldin Ismail Gawish^{a*}, Amr Arafa Mohammed Elbadry^a,
Nagat Sayed Mohammed El-Shmaa^a and Abdelraheem Mostafa Dowidar^a**

^a *Anesthesiology, Surgical Intensive Care and Pain Medicine, Faculty of Medicine, Tanta University, Egypt.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Total knee arthroplasty (TKA) is a common surgery that is associated with moderate to severe pain. Early ambulation and physical therapy are essential for functional recovery and long-term functional outcome after TKA as well as for reducing the immobility related complications. Hence, optimal pain relief while maintaining the motor function remains the mainstay in postoperative pain management after TKA.

Patients and Methods: This prospective randomized controlled open-labelled study was carried out at Tanta University Hospital, Orthopedic Surgery Department from January 2020 to February 2021.

Results: Heart rate was significantly increased at 12 and 18 hours postoperatively in group I and II compared to group III and there was insignificant change between group I and group II.

Mean arterial blood pressure was significantly increased at 12 and 18 hours postoperatively in group I and II compared to group III and was insignificant change between group I and group

II.NRS was significantly increased at 12 and 18 hours postoperatively in group I and II compared to group III and was insignificant change between group I and group II.

Patient satisfaction was significantly higher in group III compared to group I and group II on the second postoperative day.

Conclusion: Adductor canal nerve block provide better postoperative pain relieve with lower NRS after TKA than femoral and epidural blocks. It provides more stability of hemodynamic parameter and longer time for the 1st time of analgesic request. Also, total consumption of morphine in 1st postoperative day is lower than femoral and epidural blocks.

Keywords: Total knee arthroplasty; femoral nerve block; adductor canal block and epidural group.

1. INTRODUCTION

Major knee surgery such as total knee joint replacement and anterior cruciate ligament reconstruction is associated with moderate to severe postoperative pain [1]. These lower limb procedures are amenable to regional anesthesia techniques, which reduce neuroendocrine stress responses, central sensitization of nervous system, and muscle spasm, which occur in response to painful stimuli [2].

Total knee arthroplasty (TKA) is associated with severe postoperative pain leading to hypertension, tachycardia, increased O₂ demand, and myocardial stress. Pain increases sympathetic activity, releases catabolic hormones, and reduces immunity [3].

Postoperative pain is still inadequately relieved, despite substantial improvements in the knowledge of the mechanisms and treatment of pain [4]. In addition to the physiological ill effects, the presence of postoperative symptoms including pain significantly contributes to patient's dissatisfaction with their anesthetic and surgical experience [5]. It has been proven beyond doubt that inadequately treated postoperative pain may lead to chronic pain [6].

The use of epidural analgesia in management of postoperative pain following orthopedic surgeries has evolved as a critical component of multimodal approach to achieve the goal of pain relief, early mobilization, and improved compliance with physiotherapy resulting in overall improved outcome [7].

Peripheral nerve blockade is known to provide excellent postoperative analgesia after knee surgery. Several studies suggest that: pain relief is similar, and opioid-related adverse effects are less compared with intravenous patient-controlled analgesia, and similar analgesia with less hypotension compared with certain regimes

of epidural analgesia. However, femoral nerve block (FNB) reduces the strength of quadriceps muscle, which may increase the risk of postoperative falls and delay early postoperative mobilization, influencing patient satisfaction. Therefore, peripheral nerve blockade with preserved muscle function and adequate analgesic effect is desirable [8].

Adductor canal block (ACB) is a relatively new alternative for post-TKA pain management. Regional anesthesia is deposited within an adductor canal that can be easily visualized at the middle third of the thigh with use of ultrasonography. Consequently, ACB can be performed with a high success rate. Anatomical study of adductor canal showed that an adductor canal contained multiple afferent sensory nerves (e.g. saphenous nerve, medial femoral cutaneous, etc. (but only a single efferent motor nerve (vastus medialis of the quadriceps muscle (that potentially affected motor function [9].

The aim of the present study was to compare the efficacy of continuous adductor canal block, femoral nerve block or epidural analgesia in management of post-operative pain after total knee replacement.

2. PATIENTS AND METHODS

This prospective randomized controlled open-labelled study was carried out at Tanta University Hospital, Orthopedic Surgery Department from January 2020 to February 2021.

This study included 90 patients aged above 25 years of both sex, with the American Society of Anesthesiologists (ASA) classification I or II and scheduled for elective total knee replacement surgery.

Exclusion criteria were Coagulopathy, Infection at site of intervention, Hypersensitive to the study drugs, Bilateral TKA, Chronic narcotic use,

Neuromuscular disease and Previous vascular operation.

The patient was allocated according to technique used into three groups; 30 patients each; by using computer-generated software introduced into sealed closed envelopes.

2.1 Group I: Epidural Group (EG) (n:30)

Before the operation, while the patient in the sitting position, the skin of the back was prepared with iodine containing sterilizing solution, then draped in a sterile fashion and the selected level was the L2-L3 interspace. Once the injection point was marked, full aseptic preparations were undertaken. Lidocaine 2% is used to anesthetize the skin at the injection point (a subcutaneous wheal) at the midpoint between two adjacent vertebrae (midline approach). Deep infiltration in the midline and paraspinously to anesthetize the posterior structures was done. The epidural needle was inserted into the skin at this point, and advance through the supraspinous ligament, with the needle pointing in a slightly cephalad direction. Then the needle was advanced into the interspinous ligament, which is encountered at a depth of 2-3 cm. until distinct sensation of increased resistance is felt as the needle passed into the ligamentum flavum. At this point, the needle stylet was removed, and the syringe was attached to the hub of the needle. The needle was grasped with the non-dominant (left) hand and pulled toward the epidural space, while the dorsum of the left hand rested against the back. The left hand used as a "brake" to prevent the needle from advancing in an uncontrolled way. The dominant hand (right thumb) applies a slow, constant, steady pressure on the syringe plunger until loss of resistance to saline was noted. At that point, epidural catheter was placed 5 cm into the epidural space and the epidural needle was removed. After negative aspiration of blood and CSF, test dose was injected using 4 ml mixture of 2ml lignocaine 1% and 2ml epinephrine 1:100000 to detect intravascular injection, if there is tachycardia (increase heart rate 20 beat/min over resting heart rate) or increase blood pressure. Also, to detect intrathecal injection if there is immediate numbness appear in lower limb. At the end of the operation the epidural analgesia was conducted with 5 ml of 0.125% Bupivacaine, then infusion at rate of 5 ml/hr for 1st postoperative day.

2.2 Group II: Femoral Nerve Block Group (FNBG): (n:30)

At the end of the operation with the patient in the supine position, the skin over the femoral crease was disinfected and the transducer was positioned to identify the femoral artery and nerve, using the Ultrasound Machine (Philips CX50 Extreme edition) equipped with a high frequency (12 MHz) linear probe. Once the femoral nerve was identified, the needle was inserted in-plane, 1cm away from the lateral edge of the transducer in a lateral to medial orientation and advanced toward the femoral nerve. Once the needle tip was adjacent (either above, below, or lateral) to the nerve, and after careful aspiration, 1–2 mL of local anesthetic was injected to confirm proper needle placement. Proper injection pushed the femoral nerve away from the injection. Then femoral nerve catheter was inserted, and 5 ml bolus dose of 0.125% bupivacaine was injected and then infusion at rate 5 ml/hr for 1st postoperative day.

2.3 Group III: Adductor Canal Block Group (ACBG): (n:30)

The operated leg was externally rotated, the knee slightly flexed, and the thigh prepared with betadine. The medial aspect of the thigh was scanned in a transverse axial plane using the Ultrasound Machine (Philips CX50 Extreme edition) equipped with a high frequency (12 MHz) linear probe. The saphenous nerve was identified in a cross-sectional (short axis) view as it runs alongside the femoral artery in the adductor canal deep to the sartorius muscle. The probe was placed to obtain a short axis view of the femoral artery at the mid-femoral level. The saphenous nerve adjacent to the femoral artery was identified. The femoral artery was followed distally to the point at which it deviates posteriorly into the popliteal fossa. At this point, the saphenous nerve was identified as it continued in its original course just underneath the sartorius muscle. At a distance of no more than 7 cm proximal to the medial condyle, a short axis view of the sartorius and vastus medialis muscles was obtained with the saphenous nerve identified between the two muscles. Then epidural needle was advanced in plane with the ultrasound beam under real-time ultrasound guidance (in either a medial-to-lateral or a lateral-to-medial orientation) toward the target nerve.

Primary outcome: Postoperative Numeric Rating Scale (NRS) pain score to detect efficacy of block, and secondary outcomes were time of first analgesic requirement, total morphine consumption, any undesirable side effects and overall patient satisfaction with analgesia.

Premedication: Patients fasted for 6 hours for solids, 4 hours for semisolids and 2 hours for clear fluids before surgery. Patients were sedated with intravenously administered midazolam (0.02 mg/kg) before epidural placement.

2.4 Statistical Analysis

Statistical analysis was performed using the SPSS version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Parametric variables (e.g. age) were expressed as mean and standard deviation (SD) and were compared using F (ANOVA) test among the three groups with post hoc (Tuckey) test to compare each two groups. Comparison between two variables within the same group was compared by paired T test. Non-parametric variables (e.g. NRS) were expressed as median and interquartile range (IQR) and were analyzed using Kruskal-Wallis test; further analysis was performed by Mann-Whitney (U) test to compare each two groups. Comparison between two variables within the same group was compared by Wilcoxon test. Categorical variables (e.g. sex) were expressed as frequency and percentage and were statistically analyzed by Chi-square test. A two-tailed P value ≤ 0.05 was considered statistically significant.

3. RESULTS

Patients' demographic data (age, BMI, weight, sex and duration of surgery) were insignificantly different among the three groups Table 1.

Heart rate was significantly increased at 12 and 18 hours postoperatively in group I and II compared to group III ($p < 0.05$) and there was insignificant change between group I and group II. ($p > 0.05$).

There was insignificant change among the three groups at PACU, 2, 4, 6 and 24 hours postoperatively. ($p > 0.05$) Fig. 1.

Mean arterial blood pressure was significantly increased at 12 and 18 hours postoperatively in group I and II compared to group III ($P < 0.05$) and was insignificant change between group I and group II ($p > 0.05$).

There was insignificant change among the three groups at PACU, 2, 4, 6 and 24 hours postoperatively. ($p > 0.05$) Fig. 2.

NRS was significantly increased at 12 and 18 hours postoperatively in group I and II compared to group III ($P < 0.05$) and was insignificant change between group I and group II ($p > 0.05$)

There was insignificant change among the three groups at PACU, 2, 4, 6 and 24 hours postoperatively ($p > 0.05$) Fig. 3.

The total dose of morphine consumed in the 1st 24 hours was significantly decreased in group III than group I and group II. and there was insignificant change between group I and group II Table 3.

Table 1. Demographic data among the three groups

		Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	P value
Age (years)	Range	30-72	27-73	33-71	0.665
	Mean \pm SD	55.2 \pm 7.88	56.03 \pm 8.79	51.3 \pm 7.72	
Sex	Male	19 (63%)	20 (67%)	17 (57%)	0.718
	Female	11 (37%)	10 (33%)	13 (43%)	
BMI (kg/m ²)	Range	18.6-35.2	19.5-34.8	20.8-34.7	0.337
	Mean \pm SD	27.31 \pm 5.61	26.09 \pm 4.63	27.93 \pm 4.33	
ASA physical status	ASA I	22 (73%)	21 (70%)	23 (77%)	0.843
	ASA II	8 (27%)	9 (30%)	7 (23%)	
Duration of surgery (min)	Range	130-180	120-180	130-190	0.512
	Mean \pm SD	153 \pm 19.5	150.33 \pm 23.41	147 \pm 16.64	

ASA: American Society of Anesthesiologist, BMI: Body Mass Index

Table 2. Post-operative side effects in studied groups

Post-operative side effects in studied groups				
	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	P value
Nausea	9 (30%)	2 (6.7%)	3 (10%)	0.026*
Vomiting	1 (3.3%)	7 (23.3%)	4 (13.3%)	0.075
Bradycardia	2 (6.7%)	6 (20%)	5 (16.7%)	0.311
Hypotension	2 (6.7%)	1 (3.3%)	2 (6.7%)	0.809
Failed cases	2 (6.7%)	1 (3.3%)	1 (3.3%)	0.770

Table 3. Total dose of morphine consumed in the 1st 24 hours among the three groups

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)
1	8	4	4
2	5	8	10
3	8	4	4
4	12	5	4
5	4	15	4
6	4	15	4
7	4	8	5
8	10	8	20
9	4	8	8
10	5	4	4
11	5	10	4
12	10	8	4
13	5	8	4
14	4	15	4
15	8	4	4
16	10	8	4
17	12	8	8
18	8	10	4
19	5	8	4
20	8	10	4
21	8	5	4
22	8	8	5
23	8	10	5
24	8	8	4
25	10	16	4
26	4	5	8
27	8	12	5
28	8	10	5
29	4	4	4
30	20	8	4
Mean	7.50	8.47	5.30
± SD	3.43	3.46	3.19
P value	0.002*		

Overall patient satisfaction with analgesia was assessed by second anesthesiologist on the second postoperative day using a 4-point verbal scale ranging from very satisfied to very dissatisfied (1-very dissatisfied, 2- dissatisfied, 3

-satisfied, 4- very satisfied) before discharge from hospital.

Overall patient satisfaction with analgesia on second postoperative day was ranged from 4

“very satisfied” (15 patients in group I, 16 patients in group II and 25 patients in group III), 3 “satisfied” (12 patients in group I, 7 patients in group II and 5 patients in group III), 2 “dissatisfied” (1 patient in group I, 3 patients in group II and 0 patient in group III) (and 1 “very dissatisfied” (2 patients in group I, 4 patients in group II and 0 patients in group III)).

Patient satisfaction was significantly higher in group III compared to group I and group II on the second postoperative day Fig. 4.

Side effects among the three groups as vomiting, bradycardia, hypotension and failed cases were insignificantly different among the three groups Table 2.

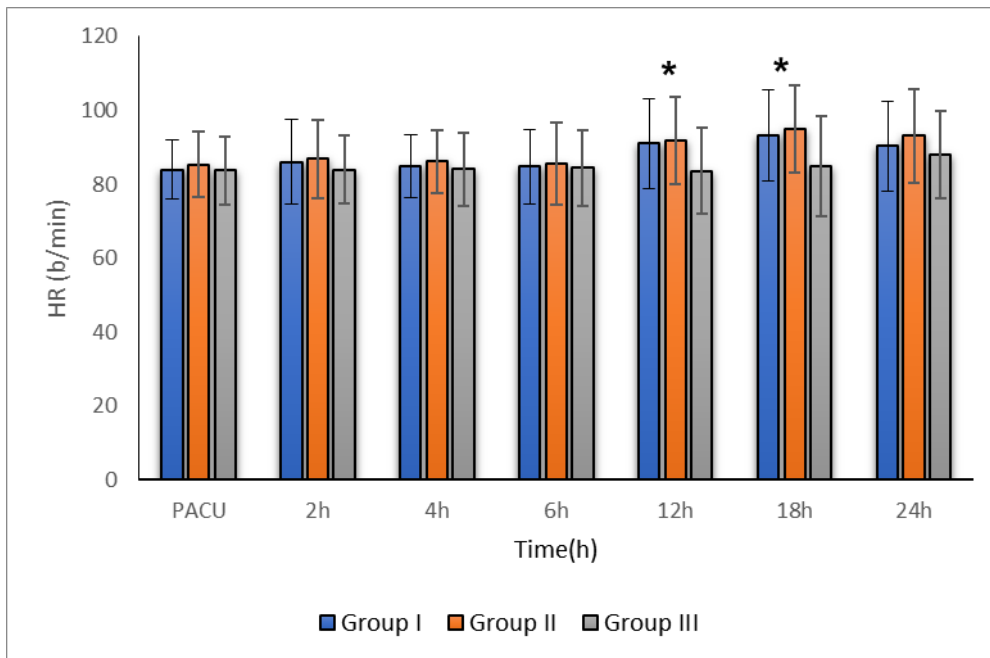


Fig. 1. Comparison between HR changes in the studied groups (b/min)

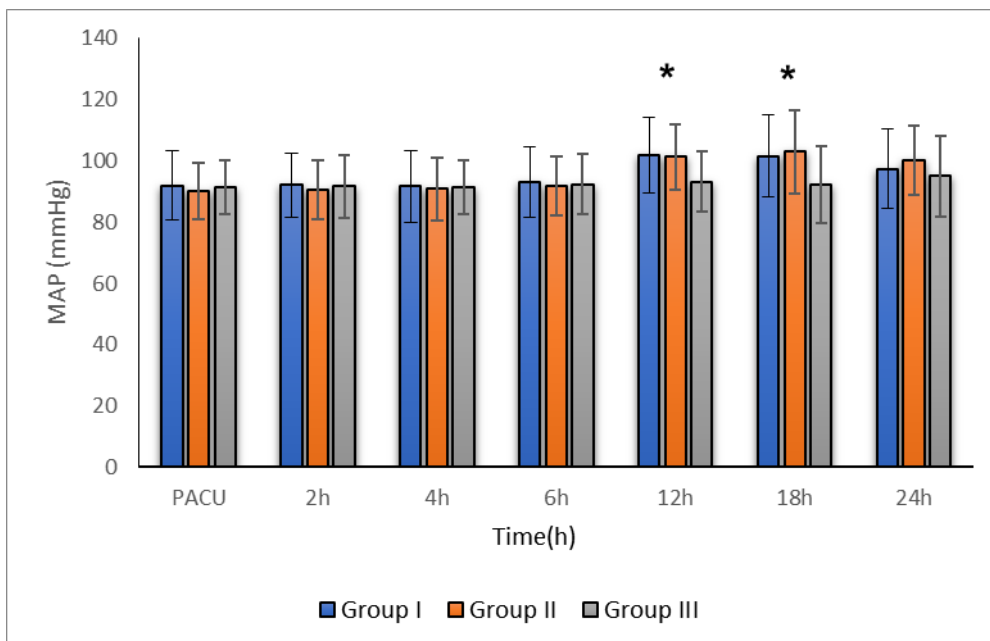


Fig. 2. Comparison between MAP changes in the studied groups (mmHg)

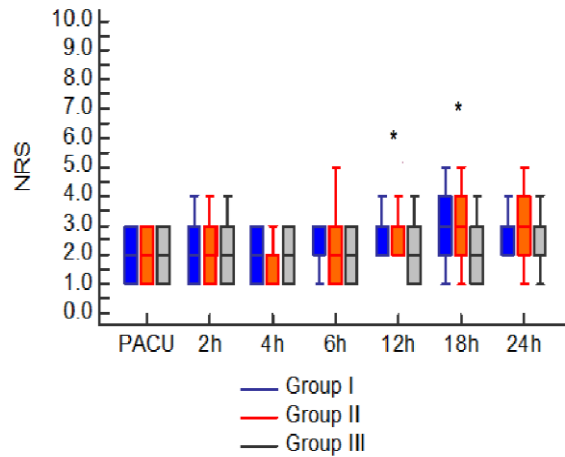


Fig. 3. Comparison between NRS changes in the studied groups

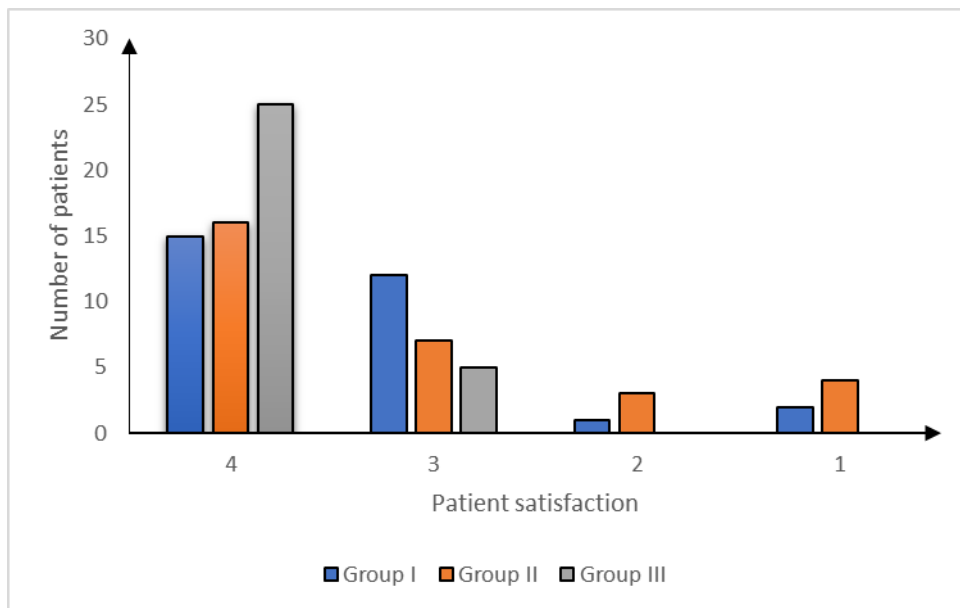


Fig. 4. Patient satisfaction in the studied groups

4. DISCUSSION

Pain is an individual experience, and the postoperative pain is difficult to predict, especially, if the level of surgical intervention differs from the initial plan [10]. Severe postoperative pain after TKA can not only be a patient suffering but also negatively affect postoperative recovery. Extensive tissue damage in major operations, such as TKA, cause immediate changes in the endocrine system and central, peripheral, and sympathetic nervous systems, and stimulate catabolic hormone release including cortisol, glucagon, growth hormone, and catecholamine, resulting in compromised immunity, increased oxygen

demand, and higher strain on the cardiovascular system [11].

Peripheral nerve blocks are associated with less pain and lower odds of unplanned hospital admission compared to systemic analgesia. The decision regarding continuous versus single injection depends on the expected surgical trauma and patient factors [12].

Among the regional analgesia techniques, continuous epidural analgesia (CEA) has been the mainstay for a considerable period. Peripheral neural blockade (femoral +/- sciatic nerve, lumbar plexus) is also used, mostly by paresthesia with or without nerve stimulation

techniques. Ultrasound guided needle and catheter placement is observed to be technically superior, with much accurate needle placement [13].

Femoral nerve block (FNB) is an analgesic technique that blocks sensation to the knee to reduce pain following surgery [13]. FNB is often considered as the gold standard for postoperative pain treatment after total knee arthroplasty. However, have been shown to reduce quadriceps muscle strength and are associated with an increased risk of falling postoperatively [14].

The adductor canal block gained attention from anesthesia and orthopedic communities. The desire to produce analgesia without loss of motor control to the thigh is beneficial. Benefits of this technique may include shorter hospital stays, earlier and more efficient rehabilitation, and pain control [15].

In our study we aimed to compare the management of postoperative pain in total knee replacement using continuous adductor canal block, femoral nerve block or epidural analgesia, evaluation of postoperative pain was the primary outcome, while total dose of analgesic consumption, first analgesic request, any undesirable side effects and overall patient satisfaction with analgesia post operatively were secondary outcomes in our study.

The studied groups were comparable regarding the demographic data (age, sex, BMI, and ASA physical status) were insignificantly different. Also, there was statistically insignificant difference as regarding the duration of surgery.

As regard the postoperative pain score (NRS); in our study; there was significant increase in NRS at 12 and 18 hours postoperatively in group I (EG) and II (FNBG) compared to group III (ACBG) and was insignificant change between group I (EG) and group II (FNBG). Also, there was insignificant change among the three groups at PACU, 2, 4, 6 hours postoperatively and significant increase at 24 hours postoperatively in the three studied groups.

In consistence with our results, Hanson et al. [16] studied the effect of the continuous adductor canal block compared with that of placebo in patients undergoing total knee arthroplasty and they concluded that, the median resting pain scores at the 18 hours was significantly reduced

for the ACB group compared with that of the other group.

Also, Kayupov et al. [17] compared the analgesic and functional outcomes between continuous ACB and epidural analgesia in TKA and showed that, patients randomized to continuous ACB group had significantly lower pain scores on 1st postoperative day compared to patients who received epidural analgesia.

Moreover, Alsheikh et al. [18] evaluated the effectiveness and early outcomes of adductor canal blockade and continuous epidural analgesia in unilateral total knee replacement and reported that, pain was significantly higher among the continuous epidural analgesia group than the adductor canal blockade group after 8 h.

On the contrary, Shanthanna et al. [19] compared continuous epidural analgesia (CEA) +fentanyl and continuous femoral block (CFB) +fentanyl for post-operative analgesia in total knee replacement. They demonstrated that, VAS scores were significantly high in the femoral group at 6 h, after which there was a declining trend, and scores were essentially similar from 24 h. This can be attributed to high dose of bupivacaine and addition of fentanyl in their study.

Also, Hegazy et al. [20] were studied patients randomized to receive either adductor canal block or femoral nerve block for total knee replacement. They noted that, there was no significant difference between the study groups regarding the NRS after 12 hours. These difference from our study can be explained by the relatively high concentration of local anesthetics used as a single dose in their study.

Moreover, Memtsoudis et al. [21] evaluated patients scheduled for bilateral total knee arthroplasty and randomized to receive ultrasound-guided FNB on one leg and ACB on the other, in addition to combined spinal epidural anaesthesia. The primary outcome was comparative postoperative pain in either extremity at 6 to 8, 24 and 48 hours postoperatively. They showed that, no significant differences were seen between extremities at any time point with regard to pain in the quantitative comparison using visual analogue scale (VAS) scores. These difference between our study can attributed to high concentration of bupivacaine and use of combined spinal epidural in both groups.

Furthermore, Armanious et al. [22] evaluated patients scheduled for uni-compartmental knee arthroplasty with combined spinal epidural anaesthesia. Patients received either FNB or ACB. They found that, no difference between the groups regarding postoperative VAS at rest except at 24 h was significantly lower in FNB group. This can be explained by the higher concentration of local anesthetics and addition of epinephrine in their study.

Concerning the time to first analgesic requirement, it was significantly increased in group III (ACBG) compared to group I (EG) and group II (FNBG) and there was insignificant difference between group I (EG) and group II (FNBG).

In contrast to our results, Abdallah et al. [23] compared the adductor canal block with femoral nerve block after anterior cruciate ligament reconstruction and they noted that, the first time to introduce morphine showed no significant difference between two groups. This can be explained by high concentration of bupivacaine and addition of epinephrine.

Regarding the total dose of morphine consumed in the 1st 24 hours was significantly decreased in group III (ACBG) than group I (EG) and group II (FNBG) and there was insignificant change between group I (EG) and group II (FNBG).

In accordance to our study, Lund et al. [24] evaluated eight patients receiving a continuous adductor canal blockade after total knee arthroplasty. They demonstrated that, the continuous adductor canal blockade for 48h after TKA was associated with low mean pain scores at rest and low mean requirements for supplemental morphine.

Also, Koh et al. [25] compared the analgesic efficacy and functional recovery between adductor canal block and femoral nerve block after total knee arthroplasty. They found that, ACB provides comparable analgesic efficacy and less total opioid consumption and also facilitates earlier mobilization by sparing quadriceps strength compared with FNB.

Inconsistence to our results, Hegazy et al. [20] and Mai et al. [12] found that, there was no significant difference between group II (FNBG) and group III (ACBG) regarding the total morphine consumption which was significantly decreased in our study in group III (ACBG).

These difference can be related to the use of relatively higher concentration of single dose of local anesthetics.

Also, Tan et al. [26] compared the total opioid consumption with adductor canal block and femoral nerve block after total knee arthroplasty. They postulated that, there was no significant difference between the ACB and FNB groups postoperatively regarding to total opioid consumption, which can be due to high concentration of bupivacaine with addition of epinephrine.

Concerning patient satisfaction, patients were very satisfied in group III (ACBG) compared to group I (EG) and group II (FNBG) on the second postoperative day.

Also, Shanthanna et al. [19] concluded that, although patients in continuous epidural group were slightly more satisfied when compared with femoral group but still statistically insignificant.

In contrast with our results, Memtsoudis et al. [21], Koh et al. [25], Tan et al. [26] and Armanious et al. [22] showed that patient satisfaction score had no significant difference between adductor canal block and femoral nerve block which can attributed to high concentration of bupivacaine and addition of epinephrine in their studies.

Regarding to side effects in our study, Nausea was significantly increased in group I (EG) than group II (FNBG) and group III (ACBG). while vomiting, bradycardia, hypotension and failed cases were insignificantly different among the three studied groups.

In agreement to our results, Hegazy et al. [20], Tan et al. [26] and Armanious et al. [22] observed that, nausea and vomiting show no significant difference between femoral nerve group (group II) and adductor canal block group (group III)

Also, Alsheikh et al. [18] showed that, the incidence of nausea and vomiting were significantly decreased after using adductor canal block compared with epidural analgesia.

In contrast to our results, Fowler et al. [1] found that, hypotension occurred more frequently among patients who received epidural than femoral nerve block and adductor canal block and there was no significant difference in the

incidence of nausea and vomiting in epidural group, femoral nerve block group and adductor canal group.

Also, Kozian et al. [27] noted that, during the first 24 hours after total knee arthroplasty, nausea and vomiting showed insignificant differences between epidural group and femoral nerve block group. Also, arterial hypotension was more frequent in the EA group in comparison with the FNB group.

Moreover, Park et al. [28] compared the benefits of continuous femoral nerve block (FNB) combined with single injection sciatic nerve block (SNB) with those of epidural analgesia for postoperative pain management after TKR. They observed that, the incidence of patients with side effects was significantly higher in the epidural analgesia group than the peripheral nerve block group.

As regard hemodynamic changes; in our study; the heart rate and mean arterial blood pressure changes showed significant increase at 12 and 18 hours postoperatively in group I (EG) and group II (FNBG) compared to group III (ACBG) and insignificant change between group I (EG) and group II (FNBG) Also, there was insignificant change among the three groups at PACU, 2, 4, 6 hours postoperatively and significant increase at 24 hours postoperatively in the three studied groups.

Although, there was a lack of literature about the comparison of continuous epidural, continuous femoral nerve block and continuous adductor canal block in hemodynamics, our study in agreement with Dauri et al. [29] who compared the effect of continuous epidural to continuous femoral block for knee surgery and revealed that, there was no significant difference in hemodynamic changes between group I (EG) and group II (FNBG).

Also, Vishwanatha et al. [30] studied continuous femoral nerve blockade (CFNB) and continuous epidural analgesia (CEA) for postoperative pain control in knee surgeries. Continuous infusion with 0.0625% bupivacaine and fentanyl 2 µg/ml started postoperatively in both groups and they found that, there was no significant hemodynamic changes between group I (EG) and group II (FNBG).

Moreover, Arjun BK et al. [31] reported that, patients received ultrasound-guided adductor

canal block and popliteal sciatic block were hemodynamically stable throughout the procedure.

5. CONCLUSION

Adductor canal nerve block provide better postoperative pain relieve with lower NRS after TKA than femoral and epidural blocks. It provides more stability of hemodynamic parameter and longer time for the 1st time of analgesic request. Also, total consumption of morphine in 1st postoperative day is lower than femoral and epidural blocks.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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