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Comparative study of epidural dexmedetomidine and epidural fentanyl with bupivacaine in total knee replacement surgeries as postoperative analgesia: An observational, double blind, randomized, clinical study

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Abstract

Background: Epidural analgesia is one of the common method for treating postoperative pain in patients undergoing total knee replacement surgeries.

The aim of the study was to compare and evaluate the postoperative analgesic effect of epidural dexmedetomidine with bupivacaine and epidural fentanyl with bupivacaine in patients undergoing total knee replacement surgeries which was done under combined spinal and epidural anaesthesia.

Material and Methods: 100 cases were included and randomly divided into two groups BD and group BF (each=50): Group BD (Dexmedetomidine group): received 5ml/hour of 0.125% of bupivacaine with 1mcg of dexmedetomidine as epidural infusion for 48 hours postoperatively

Group BF (Fentanyl group): received 5ml/hour of 0.125% of bupivacaine with 2mcg of fentanyl as epidural infusion for 48 hours postoperatively.

Statistical Analysis: Independent- Samples t test, Cross tabs and Repeated Measure ANOVA were used. SPSS for windows (version 17.0) was employed for data analysis. $P < 0.05$ was considered as significant and $P < 0.01$ was considered as highly significant.

Results: Analgesia was better in group BD than group BF with significant p value less than 0.05 Requirement of rescue analgesics significantly less in group BD than group BF ($P < 0.05$) The incidence of sedation was more in group BD as compared to group BF ($P < 0.05$) Degree of motor block was more in group BD The adverse effects like nausea and vomiting, urinary retention, pruritus, respiratory depression were less in group BD as compared to group BF ($P < 0.05$).

Conclusion: Epidural Dexmedetomidine is a good additive with bupivacaine as compared to epidural fentanyl with bupivacaine in patients undergoing total knee replacement surgeries.

Keywords: Epidural dexmedetomidine, epidural fentanyl, combined spinal and epidural anaesthesia, epidural bupivacaine, total knee replacement surgeries

Introduction

Pain is defined by the international association as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage ^[1].

Prevention and treatment of postoperative pain plays an important role. It enables early ambulation, reduces morbidity, duration of hospital stay and improves the surgical outcome. The adequacy of postoperative pain control is one of the most important factors in determining safe discharge from day care surgery ^[2]. Total knee replacement (TKR) surgeries offer a multitude of challenges for the anesthesiologist. The choice of anaesthesia has important implications for the post-operative morbidity.

Epidural anaesthesia is the most commonly used for providing intraoperative anaesthesia and post-operative analgesia in limb surgeries ^[3] and is suitable for procedures of long duration and supplementation of the drug is possible postoperatively ^[4].

Opioids are used as an additive for epidural anaesthesia with local anaesthetic like bupivacaine to synergise the anaesthetic effect ^[5] but includes the adverse effects like nausea, vomiting, pruritus, respiratory depression and urinary retention ^[6].

Dexmedetomidine is a α_2 -agonist which is highly selective and can be used as a neuraxial adjuvant. It gives stable hemodynamic conditions, provides sedation, good analgesia with minimal side effects ^[7, 8] and lacks respiratory depression thus making dexmedetomidine a safe adjuvant ^[9]

Dexmedetomidine is recent addition to the group of alpha-2 agonists which has several advantages when used epidurally [10] It acts on pre synaptic and post synaptic sympathetic nerve terminal and decreases sympathetic outflow and nor-epinephrine release which causes analgesia, arousable sedation, anti-anxiety effects, and other sympatholytic and hemodynamic effects

Dexmedetomidine may cause hypotension and bradycardia but lacks the adverse effects of opioids like nausea, vomiting, respiratory depression, pruritis [11]

Objectives

Primary Objective: to compare epidural dexmedetomidine and epidural fentanyl with bupivacaine in patients undergoing total knee joint replacement surgeries regarding quality of postoperative analgesia, sedation score, degree of motor blockade and requirement of rescue analgesics

Secondary Objective: to study side effects like hypotension, bradycardia, respiratory depression, urinary retention, nausea, vomiting, pruritis.

Methods and Materials

An observational, double blind randomized clinical study in patients undergoing elective total knee replacement surgeries done under CSE in Apollo BGS Hospitals, Mysore with study duration of one year.

The study was undertaken after obtaining an informed consent from all patients.

Ethical committee clearance was obtained.

Sample size calculation:

The number of participants required in each study group, n, was calculated using the formula as below

$$n = \frac{2 \times [Z (1-\alpha/2) + Z (1-\beta)]^2}{\Delta^2}$$

100 patients of age group between 18 to 65 years, ASA I, ASA II posted for total knee replacement surgeries were randomly divided into 2 equal groups based on shuffled, sealed, opaque envelope technique:

Group BD (Dexmedetomidine group): received 5ml/hour of 0.125% of bupivacaine with 1mcg of dexmedetomidine in each ml as epidural infusion.

Group BF (Fentanyl group): received 5ml/hour of 0.125% of bupivacaine with 2mcg of fentanyl in each ml as epidural infusion.

Postoperative epidural infusion with the drugs was continued for 48 hours

The results of our study were compared statistically using 'p' value which was obtained from student 't' test.

The anesthesiologist who was not involved in the study allotted the drugs into Group BD and Group BF to ensure double blind and equal distribution

Study drugs were prepared by a technician who was unaware of the allotment of the groups. The study drugs were prepared in the following manner:

Group BD: 75 ml of 0.5% bupivacaine and 300 mcg(3ml) of dexmedetomidine to a total of 300ml normal saline, thus giving 1 mcg/ml of dexmedetomidine with 0.125% bupivacaine.

Group BF: 75 ml of 0.5% bupivacaine and 600 mcg of fentanyl to a total of 300ml normal saline, thus giving 2

mcg/ml of fentanyl with 0.125% bupivacaine.

Infusion was started using Baxter elastomeric pump at 5ml per hour after the end of surgery.

At the end of surgery, infusion was started and was considered as 0 th hour and all patients were monitored for next 48 hours.

Observation intervals included every 2 hours for first 6 hours, every 4 hours for the next 12 hours followed by every 6 hours for next 30 hours.

All patients were given injection Ranitidine 50mg I V at bed time the previous night before surgery.

They were kept nil orally for solids for at least 6 hrs and 4 hrs for clear fluids before surgery.

On arrival of the patient to operating room, an intravenous cannula was inserted and an infusion of Ringer's lactate solution at the rate of 100 ml/hr was started to all patients.

The patients were connected to the monitor for recording Heart rate (HR), continuous electrocardiogram (ECG) monitoring, oxygen saturation, non-invasive measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP) and the Mean arterial pressure (MAP)

With patient in sitting position and under absolute aseptic precautions, Epidural space was identified using loss of resistance technique at L4-5 interspace.

Combined spinal epidural technique was employed with combined spinal needle at the same level. Subarachnoid block given using spinal needle 25-gauge pencil point and 3ml of 0.5% bupivacaine [H] was injected at a rate of approximately 0.2 mL/sec.

Epidural catheter inserted 3cms+ the depth of detecting epidural space and catheter left in the space and secured using adhesive tapes.

The surgical position was given.

Duration of the surgery noted.

After surgery, epidural analgesia using Baxter pump was started

Intravenous fluids continued in the postoperative period using I.V fluid Ringer lactate at the rate of 125ml/hour and continued upto 48 hours. All patients were catheterized intraoperatively and catheter removed after 24 hours after surgery.

Data Collected

Vitals: Heart rate, Mean Arterial Pressure

Vas: (visual analogue scale)

At the end of surgery, VAS scale (Visual analogue scale) to assess the degree of pain, with scale of 0 and 10. Scale 0 as no pain upto scale 10 as the most severe pain

Rescue analgesics

Rescue analgesic Inj. Paracetamol 1 g i. v was given when VAS score > 4.

VAS ≥ 6 was treated with Inj. Tramadol 100mg i. v and Inj. Paracetamol 1 g i. v.

Duration of effective analgesia was taken as the time interval between onset of SAB and the time to reach VAS ≥ 4.

Motor block was assessed using Bromage scale [12].

Bromage 3: unable to move feet or knees

Bromage 2: able to move feet only

Bromage 1: just able to move knees

Bromage 0: full flexion of knees and feet

Sedation using Ramsay sedation score [13].

1. Anxious or restless or both
2. Cooperative, orientated and tranquil
3. Responding to commands
4. Brisk response to stimulus
5. Sluggish response to stimulus

Hypotension was treated with intravenous (IV) doses of ephedrine 5 mg and IV fluids when there was decrease in systolic blood pressure by more than 30% from baseline

Bradycardia was treated with IV atropine 0.6 mg when the heart rate was less than 50 beats per minute

Side effects like nausea, vomiting, shivering, itching, pruritus, respiratory depression, sedation and hypotension were recorded and treated accordingly.

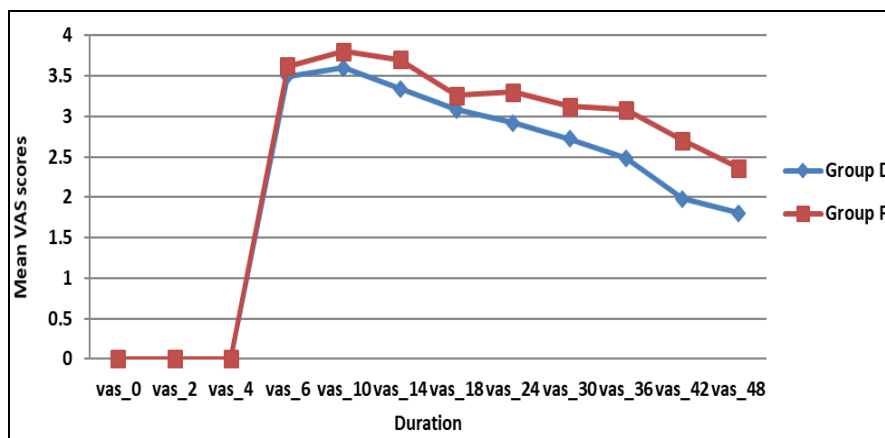


Fig 1: Showing intergroup comparison of VAS: Visual analogue score between Group BD and Group BF

The mean VAS at 0, 2, 4 th hour was .00+/-0.00 due to the effect of subarachnoid block. The mean VAS score at 6th hour was 3.50+/-0.58 and 3.62+/-0.53 in group BD and BF respectively with p value 0.283 which was not significant. The mean VAS between the 2 groups remained insignificant followed by a gradual decrease in mean VAS between the groups upto 48 hours.

At 36th, 42- and 48-hours VAS was found to be significant statistically but not clinically as patients were comfortable. Vas was found to be higher in Group BF compared to group BD. p value was insignificant throughout various intervals following epidural infusion.

Requirement of rescue analgesics

Requirement of rescue analgesics in the initial 4 hours was not necessary due to effect of subarachnoid space.

It was not significant upto 30 hours ($P > 0.05$) and highly significant at 36 hour ($p = 0.007$) showing the requirement of analgesics more in the group BF as compared to group BD. Further at 42 hour ($P = 0.023$) statistically shows significant value followed by statistically significant p at 48 hours indicating requirement of rescue analgesics more in the group BF than group BD.

The need of rescue analgesics was found to be more in Group BF when compared to group BD at various intervals of time.

Motor block

Motor blockade was complete for first 4 hours in all patients of both the groups due to effect of SAB. The motor

Results

Table 1: Showing the Demographic data of Group BD and Group BF (data are presented as mean \pm SD, number).

	Group BF	Group BD	p value
AGE (mean)	55.04+/-2.78	55.38+/- 3.36	.583
SEX	50+/-0.0	50+/-0.0	0.422
WEIGHT	58.14+/-5.34	59.06+/-4.95	0.374
HEIGHT	163.40+/-3.93	163.68+/-3.65	0.368
BMI	21.69+/-1.82	21.98+/-1.63	.411
ASA	50+/-0.0	50+/-0.0	0.423
Duration of surgery in minutes	162.28+/-5.35	161.65 +/-5.27	0.558

The groups BD and BF were comparable to each other in terms of age, height, weight and ASA physical status and duration of surgery.

Visual analogue score

blockade as assessed by Bromage scale was highly significant ($P < 0.005$) from 6th hour upto 14 hours in group BD as compared to Group BF. From 24th hour complete recovery of motor block was seen in both the groups.

Sedation score

In Group BD mean sedation score at 6, 10 hours were 2.42+/-0.73, 2.36+/-0.52 as compared to Group BF 1.98+/-0.14 and 1.95+/-0.19 respectively. Statistical evaluation between the groups showed that the patients in group BD were more sedated than the patients in group BF which is statistically significant ($p < 0.05$) and highly significant ($P < 0.001$) at 6th, 10 and 14th hour, but clinically non-significant wherein patients were sedated but responding to commands.

Discussion

The use of neuraxial opioids have many side effects such as nausea, respiratory depression, urinary retention and pruritis. Any other adjuvant which can produce equal analgesia of opioids without side effects should be an ideal adjuvant. Hence there is a need to evaluate α -2 agonists as an alternative to avoid opioid related such side effects.

Recently alpha-2 agonists like dexmedetomidine and clonidine are been used through neuraxial route for postoperative analgesia.

The pharmacologic properties of α -2 agonists have been studied and are used clinically to achieve the desired effects in regional anaesthesia. Use of these drugs epidurally cause sedation, additive analgesia, hypnosis, anxiolysis and

sympatholysis which are required for the patient.

Various studies have used epidural dexmedetomidine for postoperative analgesia through epidural route in different doses. Previous studies like Bajwa *et al.* [10], Elhakim colleagues [14], Prakash *et al.* [15] have used dexmedetomidine 1µg/kg for epidural analgesia.

Ashraf M. Eskandar and Ayman M. Ebeid [16] used infusion of bupivacaine 0.125% with 0.2 µg per kg per hour of dexmedetomidine at the rate of 5ml/ hour.

Hemodynamic changes

In our study, we noticed a significant fall in the heart rate postoperatively following infusion of dexmedetomidine at all time intervals. ($p=0.000$) This result concurs with the results of other studies on the use of epidural dexmedetomidine [17]. However this was not significant clinically. The fall in pulse rate is due to the postsynaptic activation of the alpha-2 adrenoreceptors in the central nervous system, resulting in decreased sympathetic activity, both centrally and peripherally

Lower dose of dexmedetomidine was preferred as higher doses results in more side effects such as bradycardia [18].

Changes in mean arterial pressure (MAP)

In our study the mean MAP decreased in both the groups after the start of infusion as seen by gradual drop in mean MAP over various intervals of time which was statistically not significant.

In our study, there was no significant difference between the 2 groups with respect to intraoperative and postoperative MAP with $P>0.05$. The drop in MAP of both the groups were clinically not significant. Thus, the hemodynamic stability with respect to MAP was maintained even in the presence of Dexmedetomidine.

It correlates with the study by Bajwa *et al.* [10] who found that the mean values of MAP were comparable between the groups throughout the study duration.

Paula F Salgado *et al.* [18] also observed that groups in their study had comparable hemodynamics throughout the period of study.

As long as patient's volume status is maintained, dexmedetomidine does not produce significant fall in blood pressure. As the patients were preloaded with adequate intravenous fluids prior the neuraxial block and postoperatively maintained with intravenous fluids, the drop in MAP was not significant ($P>0.05$).

Visual analogue score

Vas was higher in Group BF as compared to group BD. p value was insignificant throughout various intervals following epidural infusion. This correlates with study of Bajwa *et al.* [10], Elhakim and colleagues [14], Jain D and colleagues [19], Selim and colleagues [20], Gupta K *et al.* [21] where prolonged postoperative analgesia was seen in dexmedetomidine group showing better analgesia compared to fentanyl group.

Sedation Scoring

Sedation score between the groups showed that the patients in group BD were more sedated than the patients in Group BF which is statistically significant ($P<0.05$), but clinically non-significant. This concurs with Bajwa *et al.* [10], Prakash *et al.* [15], Karhade SS and colleagues [22] Dexmedetomidine is known to produce arousable sedation

by its action on locus coeruleus nucleus without producing any respiratory depression. This effect of dexmedetomidine is a welcome side effect in the post-operative period as the patient will remain calm and free of anxiety. No patient in our study in the group BD had any post-operative respiratory depression as there was no change in the SPO₂, breathing room air.

The maximum Ramsay sedation scores were higher (>3) in patients of dexmedetomidine group while it was less than 2 in patients of fentanyl group. No patient needed any supplemental sedation during surgery.

Bromage scale

Motor blockade was complete for first 4 hours in all patients of both the groups due to effect of SAB. The motor blockade as assessed by Bromage scale was highly significant ($P<0.005$) from 6th hour upto 14 hours in group BD as compared to Group BF. From 24th hour complete recovery of motor block was seen in both the groups.

The higher Bromage score noted in group BD in our study correlates with the motor block intensity in the previous studies by Bajwa *et al.* [10], Prakash *et al.* [15], Gupta K *et al.* [21], where motor blocks were more pronounced in the dexmedetomidine group

Rescue analgesics

The requirement of rescue analgesics was more in Group BF when compared to group BD at various intervals of time. This was similar to results of Bajwa *et al.* [10], Elhakim and colleagues [14], Gupta K *et al.* [21], Karhade SS and colleagues [22] where there was decreased requirement of analgesics in dexmedetomidine group.

Side Effects

Mild pruritis was observed in 4 patients of Group BF which required no treatment.

The ventilatory frequency and peripheral oxygen saturation were comparable between groups.

Three patients suffered from nausea in Group BF which was treated symptomatically.

Two patients in Group BF had shivering, which was managed with Inj. Tramadol i. v 25mg.

Complete recovery of sensory and motor function was observed in all the studied patients and all patients followed up after two weeks after surgery.

No patient suffered from urinary retention and the bowel recovery was not altered.

There were no transient neurological symptoms in any patient.

All the patients had peripheral oxygen saturation greater than 95% at all times and did not require additional oxygen.

No patient had respiratory rate below 10/ min.

Limitations of Our Study

Ideally we should have started study infusion in the postoperative period only after the patient has developed significant pain with $vas>4$. In our study we started the infusion immediately after the surgery irrespective of VAS score. This may alter the effective difference between fentanyl and dexmedetomidine regarding the efficacy of analgesia and other variables like motor block and sensory block.

Dense motor block in group BD hindered mobilization, active physiotherapy in the first 24 hours.

Conclusion

The use of 1 µg dexmedetomidine as epidural infusion postoperatively is an attractive alternative as an additive to bupivacaine as compared to fentanyl with bupivacaine in patients undergoing total knee replacement surgeries in providing good quality of postoperative analgesia with minimal side effects.

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