Comparison of Effect of Epidural Bupivacaine, Epidural Bupivacaine Plus Fentanyl and Epidural Bupivacaine Plus Clonidine on Postoperative Analgesia after Hip Surgery

Rakesh Karnawat1*, Swati Chhabra2, Sadik Mohammed3 and Bharat Paliwal3
1 Department of Anaesthesiology, Dr S N Medical College, Jodhpur, Rajasthan, India
2 Department of Anaesthesiology, Medical College, Rohtak, Haryana, India

Abstract

Background: Management of postoperative pain is one of the most challenging and gratifying domains of anaesthesia. Search for an ideal adjuvant for post operative epidural analgesia still continues.

Methods: A total of 75 healthy patients of both sexes in age group 50-80 years belonging to ASA status I and II posted for elective hip surgeries were enrolled and randomly divided into three groups of 25 each - Group B, Group BF and Group BC. All the patients in the three groups received 3.5 ml Bupivacaine heavy (0.5%) intrathecaally before surgery, followed by epidural bolus postoperatively, at ‘two segment sensory regression’ in following manner: initial bolus made to 10 ml with each group given - 7 ml of 0.125% Bupivacaine and 3 ml distilled water with adjuvant as 50 μg Fentanyl in group BF and 100 μg Clonidine in group BC. Top up of 7 ml was given to each group with 5 ml of 0.125% Bupivacaine and 2 ml distilled water with adjuvant as 50 μg Fentanyl in group BF and 75 μg Clonidine in group BC.

Results: There was no statistically significant difference between the demographic profile. VAS scores were found to be better in Group BF and BC at most of the times and these scores were significantly lower than Group B. Rescue analgesia was required in 12% patients in Group B while none of the patients in Group BF or Group BC required rescue analgesia. Nausea, vomiting and pruritus were observed in 52% of the patients in Group BF and in none of the patients in Group BC and Group B. Degree of sedation was significantly more in Group BC when compared with Group BF and Group B.

Conclusion: Combination of Bupivacaine-Clonidine was found to be a better option than Bupivacaine-Fentanyl for postoperative epidural analgesia in hip surgery patients.

Keywords: Postoperative pain; Combined spinal epidural; Bupivacaine; Fentanyl; Clonidine

Introduction

Management of postoperative pain is one of the most challenging and gratifying domains of anaesthesia. Any method of postoperative analgesia must meet three basic criteria: it must be effective, safe and feasible. Despite advances in knowledge of pathophysiology of pain, pharmacology of analgesics and development of effective techniques for postoperative pain control, many patients continue to experience considerable discomfort [1,2]. The majority of patients after surgery managed with parenteral drugs are left with unrelieved pain [3].

A variety of neuraxial (primarily epidural) and peripheral regional analgesic techniques may be employed for the effective treatment of postoperative pain. In general, these techniques can provide superior analgesia (especially when local anesthetics are used) compared with systemic opioids and use of these techniques can even reduce morbidity and mortality. Effective treatment of postoperative pain blunts autonomic, somatic and endocrine responses.

Poorly controlled acute postoperative pain may be an important predictive factor in the development of pathologic long-term chronic pain after surgery [4,5]. Control of acute postoperative pain may improve long-term recovery or patient-oriented outcomes (e.g., quality of life). Patients whose pain is controlled in the early postoperative period (especially with use of continuous epidural or peripheral catheter techniques) may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery [6,7].

Epidural infusion of local anesthetic alone may be used for postoperative analgesia. However, epidural local anesthetic drugs administered alone have never become widely used for routine postoperative analgesia because of the significant failure rate resulting from regression of the sensory block and the unacceptable incidence of motor blockade and hypotension [8]. A variety of adjuvants may be added to epidural infusions to enhance analgesia while minimizing the side effects and these include mainly Opiates, Ketamine, Clonidine, Benzodiazepines etc. But no single drug has proved to be devoid of any side effect. So, search for an ideal adjuvant still continues that could result in reliable prolongation of postoperative pain relief without side effects.

Bupivacaine is a long-acting, effective local anaesthetic that is commonly administered by the epidural route for the relief of postoperative pain. The concentration of bupivacaine exceeding 0.125% may be associated with excessive motor blockade when used in epidural infusions in the lumbar region [9].

*Corresponding author: Dr. Rakesh Karnawat, Professor, Department of Anaesthesiology, Dr S N Medical College, Jodhpur, Rajasthan, India, Tel: 09828033321; E-mail: dr.rakeshkarnawat@yahoo.com

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The use of epidural analgesia for pain relief was revolutionized by the use of epidural opioids after the discovery of opioid receptors in the dorsal horn of the spinal cord [10]. Opioids have both presynaptic and postsynaptic effects in the dorsal horn and affect the modulation of nociceptive input but do not cause motor or sympathetic blockade. A synergistic effect between local anesthetic and opioids has been demonstrated in animal models, in which the antinociceptive effects of opioid and local anesthetic mixtures were greater than those of opioid or local anesthetic alone [11].

α-Adrenergic agonists produce pain relief through an opioid independent mechanism and may be used as alternatives to opioids for combination with local anesthetics for epidural analgesia [12]. Clonidine is an imidazoline derivative with α₂-adrenergic agonistic activity which, when administered by the epidural route, has analgesic properties and potentiates the effects of local anesthetics [13].

Studies have been done in the past to ascertain the optimal doses and concentrations of epidural local anesthetics, opioids and other adjuvants so as to get the best of the postoperative epidural analgesia and the least of the side effects [14-16].

Aims and Objective

The present study was conducted to assess the postoperative analgesia obtained with epidural Bupivacaine, epidural Bupivacaine-Clonidine and epidural Bupivacaine-Fentanyl with the following aims:

1. To compare the efficacy of the three groups for postoperative analgesia.
2. To compare the time required for first epidural top-up after bolus dose.
3. To compare the number of doses of rescue analgesic.
4. To compare the side-effects of the three groups.

Material and Methods

This prospective randomized double blind study was conducted after obtaining Institutional Ethics Committee approval and written informed consent. The person giving the drug and the monitoring personnel were blinded. The infusion drug was prepared by the author and named 1 for Group B, 2 for Group BF and 3 for Group BC. A total of 75 healthy patients of both sexes posted for routine elective hip surgeries were enrolled and randomly divided into three Groups: Group B (n=25), Group BF (n=25) and Group BC (n=25).

All the patients in the three groups received 3.5 ml Bupivacaine heavy (0.5%) intrathecally before surgery, followed by the epidural bolus postoperatively, at ‘two segment sensory regression’ and epidural top up when VAS was more than 4, in the following manner:

Group B: Bolus - 7 ml of 0.125% Bupivacaine +3 ml distilled water.

Top up - 5 ml of 0.125% Bupivacaine +2 ml distilled water.

Group BF: Bolus - 7 ml of 0.125% Bupivacaine +50 µg Fentanyl made to 3 ml with distilled water. Top up - 5 ml of 0.125% Bupivacaine +30 µg Fentanyl made to 2 ml with distilled water.

Group BC: Bolus - 7 ml of 0.125% Bupivacaine +100 µg Clonidine made to 3 ml with distilled water. Top up - 5 ml of 0.125% Bupivacaine +75 µg Clonidine made to 2 ml with distilled water.

Patients posted for elective hip surgery in the age group 50-80 years belonging to ASA physical status I and II were included in the study. Patients not willing to be a part of the study, having known allergy or addiction to study drugs, in whom central neuraxial block was contraindicated (local infection, shock, raised intracranial tension, spinal deformity, neurological disorder etc.) or patients on anticoagulant therapy or having coagulopathy were excluded from the study.

Every patient was assessed properly and in detail one day prior to surgery. Patients were instructed to undergo overnight fasting before surgery. On entering the OT, standard monitoring including NIBP, Pulse oximetry and ECG leads was attached to the patient. Baseline SBP and heart rate were recorded by taking the mean of 3 consecutive readings taken 1 min apart. I.V. access was established using a 16/18 G cannula and preloading was done with ringer’s lactate solution at a dose of 15 ml/kg.

All patients underwent surgery with a combined spinal epidural (CSE) block with the needle through needle technique using a single interspace. Under all aseptic precautions, an 18-gauge Tuohy needle was introduced into the epidural space at the L2-L3 or L3-L4 interspace using the loss-of-resistance technique and an epidural test dose with 60 mg of lignocaine and 15 µg of epinephrine was then injected and observed for any motor block or rise in heart rate. Then a spinal needle was placed through the Tuohy needle into the subarachnoid space. After return of clear cerebrospinal fluid, patients received a single intrathecal injection of 3.5 ml Bupivacaine (heavy) 0.5%. After the intrathecal injection, the spinal needle was withdrawn and an epidural catheter was threaded 3-5 cm into the epidural space. The Tuohy needle was withdrawn and the catheter secured before the patient was positioned appropriately for the surgery. No medications were administered via the epidural catheter until a “two segment sensory regression” from the spinal anesthesia was observed.

Bolus epidural drugs were administered postoperatively at “two segment sensory regression” time. The study period commenced at the time of injection of epidural bolus dose (Time 0 min) and terminated at 24 hours postoperatively. All the parameters were recorded at 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr & 24 hrs postoperatively. Top-up doses of drugs were administered epidurally whenever the VAS score became more than 4. VAS of less than 4 cm was considered as effective analgesia, 4-7 was considered ineffective analgesia and VAS of 7 or more was considered as failure of technique.

Rescue analgesic (Diclofenac sodium, 75 mg) was injected deep intramuscularly, when patients complained of inadequate analgesia even after 3 successive top-up doses given 20 minutes apart [17].

Bradycardia was defined as pulse rate<60 beats per minute and hypotension was defined as reduction of MAP ≥ 30% of baseline. Inj. Mephentermine 6 mg iv bolus was given and repeated as necessary. Similarly, if pulse rate decreased to less than 60/min, Inj. Atropine 0.3 mg iv was given and interventions were recorded. Respiratory rate, sedation score and arterial oxygen saturation were monitored to assess respiratory depression, which was defined as a fall of respiratory rate to 8 breaths or less per minute or a sedation score of 4 or a fall of arterial oxygen saturation value to less than 90%. Any patient having respiratory rate less than 8/min and SpO₂ less than 90% was given supplemental oxygen with a ventimask at the rate of 5 liters/min. Bromage scale was used for the assessment of motor blockade. Side effects like nausea, vomiting, itching, urinary retention etc were observed. The number of doses of epidural top ups and rescue analgesic required was recorded for each group.

For statistical analysis, Arithmetic mean, Standard Deviation, ANOVA, Chi Square test and P-value were used using INSTAT statistical software.
Results

There was no statistically significant difference between the demographic profile (age, height and weight), ASA physical status, baseline heart rate and mean arterial pressure of the three groups (Table 1).

VAS scores (Figure 1) were found to be better in Group BF and BC at most of the times and these scores were significantly lower than Group B (P<0.05) at 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr and 24 hr. However, no significant difference was observed between Group BF and Group BC (P>0.05) at 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr and 24 hr.

No significant difference was seen in Bromage Scale (Figures 2 and 3) in the three groups at 0 min, 15 min, 30 min, 1 hr, 8 hr, 12 hr, 18 hr and 24 hr (P>0.05). At 2 hr, statistically significant difference was observed between Group B and Group BF. At 4 hr, statistically significant difference was observed between Group B and Group BF; Group B and Group BC. Although none of the patients had grade 3 motor blockade in any of the groups.

Number of epidural top ups required in Group B was significantly more than that required in Group BF and Group BC (p<0.05). However, number of top ups required in Group BF and Group BC were comparable (p>0.05). Rescue analgesia was required in 12% patients in Group B while none of the patients in Group BF or Group BC required rescue analgesia (Table 2).

Nausea and vomiting was observed in 52% of the patients in Group BF and in none of the patients in Group BC and Group B. Pruritis was observed in 48% of the patients in Group BF and in none of the patients in Group BC and Group B. Retention of urine was observed in 12% of the patients in Group B, 24% of the patients in Group BF and 8% of the patients in Group BC (Table 3).

Discussion

Effective pain control is essential for optimal care of surgical patients. Surgery produces tissue injury with consequent release of histamine and inflammatory mediators [18]. The release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of the nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of neurotransmitters (i.e., substance P and calcitonin gene-related peptide) in the periphery induces vasodilatation and plasma extravasation.

During spinal and epidural anaesthesia, the applied drugs diffuse directly into the spinal cord, particularly to superficial neurones in laminae I and II of the dorsal horn. Most fine calibre C- and A-fibres terminate within laminae I and II [19,20] and are therefore considered to be a key element in the nociceptive processing system.

Fentanyl has emerged as a suitable opioid for infusion into epidural space. Advantages of fentanyl over other opioids are that, it is more lipophilic, easily crosses lumbar dura and quickly penetrates the lipid phase of underlying tissue of the cord.
antinociception may be reversed by spinal administration of Idazoxan, colleagues [22] have demonstrated in sheep that clonidine-induced α2 adrenergic receptors located in the spinal cord [21]. Eisenach and colleagues 

The mechanism of analgesia may be a direct effect of Clonidine on α2 adrenergic receptors located in the spinal cord [21]. Eisenach and colleagues [22] have demonstrated in sheep that clonidine-induced antinociception may be reversed by spinal administration of Idazoxan, a α2 adrenergic antagonist.

The present study has demonstrated that Bupivacaine-Fentanyl and Bupivacaine-Clonidine combination causes equivalent post operative analgesia in hip surgeries with intermittent epidural administration; although they differ in the side effect profile. Also, we found that the two combinations were superior to plain Bupivacaine when given epidurally for postoperative analgesia. These results are in accordance with previous study by Topcu et al. [23], who found that addition of Clonidine or Fentanyl to local anaesthetics for PCEA after abdominal hysterectomy can reduce analgesic demand. However, Kizilarslan et al. [24] compared epidural Fentanyl-Bupivacaine with Clonidine-Bupivacaine for analgesia in labour and found that combination of Bupivacaine and Clonidine provides satisfactory analgesia for first-stage labour, and of longer duration than Bupivacaine-Fentanyl. Also, Cooper et al. [25] found epidural Bupivacaine-Fentanyl combination to be better than Bupivacaine alone for postoperative analgesia. Milligan et al. [26], Mogensen et al. [27], Klimscha et al. [28], O’Meara et al. [29], Carabine et al. [30] found an enhanced effect of epidural Bupivacaine-Clonidine combination when compared with Bupivacaine alone.

There was no statistically significant difference between the demographic profile (age, sex, height, weight) of the three groups (p>0.05). All the patients selected were from ASA physical status Class I and II, this was statistically similar in the three groups (p>0.05).

In this study, VAS scores were found to be better in Group BF and BC at most of the times and these scores were significantly lower than Group B (p<0.05) at 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr and 24 hr. However, no significant difference was observed between Group BF and Group BC (p>0.05) at 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr and 24 hr. Giovanni Cucchiaro et al. [31] had also concluded in their study that epidural clonidine has same safety and analgesic efficacy as epidural fentanyl when combined with a local anaesthetic.

Degree of motor blockade (assessed in this study by Bromage scale) was significantly more in Group B than in Group BF or Group BC (p<0.05) at 2 hr and 4 hr. This is of importance as any degree of motor blockade in the postoperative period could be troublesome for the patient and this also can become an obstacle if early mobilization for postoperative rehabilitation is desired. Excessive lower limb motor blockade with controlled infusion of epidural LAs is uncommon, occurring in only in 3.0% of cases using low concentrations of Bupivacaine. [32] If intense motor blockade does occur, it may result in the development of pressure areas on the heels [33-35] and deep venous thrombosis [36]. Epidural blockade has been blamed in occasional case reports for masking the symptoms of compartment syndrome [37-39], although there have also been cases which have been diagnosed successfully during epidural blockade [40]. So, this should be considered while selecting a drug, its dose/concentration for postoperative analgesia.

Nausea and vomiting was observed in 52% of the patients in Group BF and in none of the patients in Group BC and Group B. Pruritis was observed in 48% of the patients in Group BF and in none of the patients in Group BC and Group B. Retention of urine was observed in 12% of the patients in Group B, 24% of the patients in Group BF and 8% of the patients in Group BC. The incidence of nausea and vomiting, and that of urinary retention are comparable to previous studies by Berti et al. [41], O’Meara et al. [29] and Cooper et al. [25].

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*Sedation Scale: I: Awake and fully alert; II: Awake but drowsy; III: Sleeping but easily arousable; IV: Sleeping but difficult to arouse; V: Unresponsive to verbal or tactile commands.

Table 4: SEDATION* (No. of patients in each sedation grade).
Degree of sedation was significantly more in Group BC when compared with Group BF and Group B (P<0.05) at 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 18 hr and 24 hr. Most of the patients were either 'Awake but drowsy' or 'Sleeping but easily arousable'. This degree of sedation was not troublesome for the patients and they were quiet, eyes closed, but were able to answer immediately and accurately when questioned by the observer. Drowsiness did not interfere with measurement of pain. Drowsiness is caused by the action of clonidine on α2 adrenergic receptors in the brainstem [42].

Rescue analgesia was required in 12% patients in Group B while none of the patients in Group BF or Group BC required rescue analgesia. Number of epidural top ups required in Group B was significantly more than that required in Group BF and Group BC (P<0.05). However, number of top ups required in Group BF and Group BC were comparable (P>0.05).

Conclusion

This study concluded that combined Bupivacaine-Fentanyl and Bupivacaine-Clonidine provided equivalent postoperative epidural analgesia in hip surgery patients which was more than that with Bupivacaine alone. Combination of Bupivacaine-Clonidine had a better side effect profile than combined Bupivacaine-Fentanyl.

Thus, combination of epidural Bupivacaine-Clonidine was found to be a better option than epidural Bupivacaine-Fentanyl for postoperative analgesia in hip surgery patients.

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