Section: Anaesthesiology and Critical Care

Original Research Article

COMPARATIVE STUDY ON THE ANALGESIC EFFICACY OF EPIDURAL MORPHINE AND EPIDURAL MORPHINE WITH BUPIVACAINE FOR POSTOPERATIVE ANALGESIA IN LOWER LIMB SURGERY

Dilip Ingudum[1], Ashem Jack Meitei[1], Yumnam Arunkumar Singh[1], Khulem Maniram Singh[1], Binarani Maharabam[1], Raghupathi Ramaswamy[1], Millo Tama[1]

[1]Department of Anaesthesiology and Critical Care, Regional Institute of Medical Sciences, Imphal, Manipur, India.

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Corresponding Author:
Dr. Ashem Jack Meitei
Email: jack2k49@gmail.com

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Abstract

Background: Epidural injection of local anaesthetic alone has never become widely used for postoperative pain management because of various unsatisfactory reasons. Morphine is a potent analgesic; it can be administered epidurally either alone or in combination with bupivacaine. Aims and Objectives: To compare the effect and duration of postoperative analgesia between epidural morphine and epidural morphine with bupivacaine in patients undergoing lower limb surgery. **Material & Method:** In this randomized, double-blinded study on 50 patients between 20 and 60 years of age belonging to ASA I and II were randomly allocated to receive combined spinal epidural analgesia (CSEA), Group A (n=25)– Morphine 1mg (2 ml) diluted up to 10 ml normal saline, Group B (n=25) – Morphine 1mg (2ml) + Bupivacaine (0.125%) 8 ml. Haemodynamic and respiratory parameters were monitored following epidural bolus and top-up. Groups were compared for pain intensity and relief of pain, duration of postoperative analgesia, and adverse events for 24 hrs after surgery. **Results:** Haemodynamic and respiratory changes after epidural bolus and epidural top-up in both groups were comparable. Duration of analgesia following epidural bolus was longer in Gr-B (13.99±0.95) than Gr-A (9.78±1.73) by 4.21 hrs, and following epidural top-up was longer in Gr-B (17.15±1.11) than 12.05±1.82) by 5.10 hrs respectively, $P < 0.001$. Pruritus developed in 2 patients (8%) in Gr-A and 1 patient (4%) in Gr-B, $p > 0.005$. **Conclusion:** Epidural morphine plus bupivacaine has a longer duration of analgesia as compared to epidural morphine alone for postoperative analgesia in lower limb surgeries without significant side effects.

INTRODUCTION

Management of postoperative pain is one of the most challenging and gratifying domains of anaesthesia. Any method of postoperative analgesia 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] The discovery of opioid receptors in the brain and spinal cord started a new era in the field of postoperative analgesia.[4]

It is possible to perform all the surgical procedures in the lower abdomen as well as lower extremities under spinal anaesthesia. In spite of various parenteral drugs, most of the patients operated under spinal anaesthesia could not be relieved from acute postoperative pain.

CSEA is one of the techniques of anaesthetic armamentarium, which can be used as a sole technique for carrying out surgical procedures and postoperative pain management using various drug regimes.[5]

Bupivacaine is a long-acting, effective local anaesthetic that is commonly administered by the epidural route for the relief of postoperative pain.[6]

Epidural administration of local anaesthetic alone may be used for postoperative analgesia. However, epidural local anaesthetic drugs administered alone

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have never become widely used for routine postoperative analgesia because of the significant failure rate resulting from regression of the sensory block and unacceptable incidence of motor blockade and hypotension.[7] Opioids can be either administered epidurally alone or in combination with bupivacaine.[8] Epidural administration of opioids in combination with local anaesthetic agents in low doses offers a new dimension in the management of postoperative pain.[9]

A variety of adjuvants may be added epidurally to enhance analgesia while minimizing the side effects and these include morphine, fentanyl, clonidine, dexmedetomidine, midazolam and ketamine. But no single drug has proved to be devoid of any side effects.[10]

The purpose of this study is to evaluate the duration of postoperative analgesic effect and associated complications of epidural morphine alone and a combination of morphine with bupivacaine in patients undergoing lower limb surgery.

MATERIALS AND METHODS

This randomized double-blind prospective study was conducted at RIMS Hospital, Imphal between October 2016 and September 2018. Approval from the ethical committee of the Regional Institute of Medical Sciences, Imphal (Ref No. A/206/REB-Comm(SP)/RIMS/2015/191/59/2016) was obtained.

Inclusion criteria: Patients with ASA I and II, aged 20-60 years of either sex with informed consent, who were posted for elective lower limb surgeries under combined spinal epidural anaesthesia (CSEA) were enrolled.

Exclusion Criteria

1. ASA grade III and above
2. Patients under anticoagulant therapy
3. Patients with vertebral column disease or backache,
4. patients with any neurological or psychotic disorder, difficulty in communication.
5. Patients with septicaemia or viral disease.
6. Patients with marked hypovolaemia, dehydration, and severe anaemia.
7. Patients who were opioid dependent.
8. Patients who refuse to give informed consent.

The sample size was calculated based on a previous study by Bhattacharyya et al.[11] assuming the mean duration of analgesia in minutes, µ1=206.8 minutes, µ2=507.3 minutes, sigma = 163.05 minutes, a sample size of 7 was calculated using web-based sample size calculator in each group with α value of 0.05 and power of study 0.9. Even though the calculated sample size was very small, the morphine was reduced to a minimum in the present study and was rounded to 25 patients in each group.

Randomization: Patients were randomly assigned through a computer-generated random number list with assigned numbers scaled in envelopes, to the Morphine group (Group A) or to the Morphine combined with Bupivacaine group (Group B). Study drugs were prepared by an anaesthesiologist not involved in the study in a coded syringe to keep the study investigator and the patients blinded.

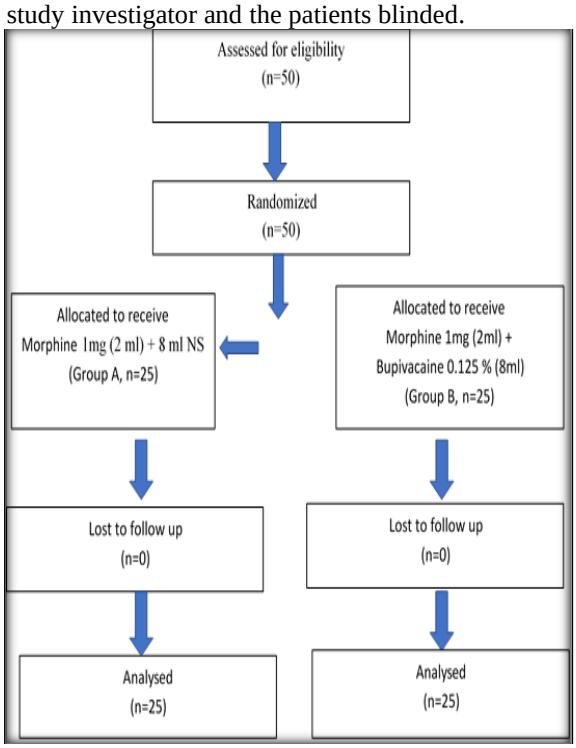

Figure 1: CONSORT (Consolidated Standards of Reporting Trials) diagram.

Study Procedure

Pre-anaesthetic evaluation was conducted uniformly and all the participants were kept nil orally preoperatively.

In the operating room, routine ASA monitors were attached to the patients and baseline heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) and peripheral oxygen saturation (SPO2) were recorded. An 18 G intra venous cannula was secured on the dorsum of the hand and preloaded with ringer's lactate, 15 ml per kg body weight about 15 minutes before the intended time of spinal anaesthesia.

All the patients were positioned in the lateral decubitus position and after adequate aseptic precautions 18G Tuohy epidural needle was introduced in L3-L4 interspace. The epidural space was identified by loss of resistance to air. Then the epidural space was cannulated with an epidural catheter, advancing for not more than 4 to 5 centimetres. An epidural test dose with 3 ml of 2% injection lignocaine with adrenaline was injected through the epidural catheter to rule out any motor block or rise in the heart rate.

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All the patients in both groups received 2.5 ml of 0.5% bupivacaine (heavy) intrathecally at L4-L5 interspace with a 25G spinal needle to perform the scheduled operation.

Patients in group A received 1mg (2 ml) of injection morphine diluted up to 10 ml of normal saline. And Patients in group B received 1mg (2 ml) of injection morphine with 8 ml of 0.125% bupivacaine.

Postoperative pain intensity and relief of pain after epidural drug administration were evaluated by the Verbal Rating Scale (VRS).[12]

A bolus dose of one of the study drugs was administered in the epidural catheter postoperatively when the patient complains of mild pain (VRS=1). Subsequent top-up doses were maintained with the same drug and the same doses in each group when the patient complains of mild pain (VRS=1).

Duration of analgesia, as well as the requirement of additional top-up analgesic, was noted for 24 hours after surgery and measured as the time between the epidural bolus and the time when the patient complains of mild pain (VRS=1). After the epidural bolus and top-up doses of the study drugs, a decrease in mean arterial pressure (MAP) of > 20% of baseline, was treated with rapid infusion of 500 ml of ringer's lactate and injection Mephentermine and a decrease in heart rate < 50 beats/minute were treated with injection atropine intravenously.

The Parameters measured were:

Primary

a. Duration of analgesia after administration of epidural bolus and top-up of study drugs.

Secondary

a. HR, SBP, DBP, mean arterial pressure (MAP), and SPO2 one minute before and one minute after the administration of epidural bolus as well as epidural top-up drugs.
b. Adverse effects like nausea, vomiting, itching, bradycardia & hypotension during 24 hours following bolus epidural and top-up administration.

Data were analysed using SPSS version 23.0 (Armonk, NY: IBM Corp.). Descriptive statistics like mean and standard deviation were used. For continuous variable, student t-test was used for comparison between the two groups. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic variables were comparable between the two study groups (Table/Fig 2) (p>0.05).

Table 1: Demographic parameters

Parameters	Mean + SD		P- value
	Group A (n=25)	Group B (n=25)	
Age (years)	36.76 ± 12.72	38.28 ± 15.08	0.700
Sex: Male/Female	23/2	19/6	0.269
Weight (Kg)	63.80 ± 5.78	61.16 ± 5.24	0.097
Height (cm)	165.16 ± 5.85	162.28 ± 6.49	0.575
ASA grade I : II	25:0	23:2	0.776

Table 3: Pre-anaesthetic haemodynamic and respiratory variables

Haemodynamic and respiratory variables	Group A Mean ± S.D.	Group B Mean ± S.D.	P-value
HR/Minute	83.48 ± 14.72	80.08 ± 8.98	0.329
SBP (mmHg)	130.96 ± 6.66	129.88 ± 7.47	0.593
DBP (mmHg)	85.04 ± 5.97	83.16 ± 5.66	0.259
MAP (mmHg)	100.00 ± 5.66	98.56 ± 5.30	0.359
SPO2 (%)	99.12 ± 1.13	99.00 ± 1.29	0.728

Mean pre-anaesthetic haemodynamic and respiratory variables between the two study groups (Table/Fig 3) were comparable and found statistically insignificant (P> 0.05).

Table 4: Mean haemodynamic and respiratory variables 1 minute before and 1 minute after epidural bolus administration

Haemodynamic and respiratory variables	Group A Mean ± S.D.	Group B Mean ± S.D.	P-value
HR before the epidural bolus	82.52 ± 6.56	83.44 ± 9.47	0.692
HR after the epidural bolus	80.12 ± 6.80	81.44 ± 8.25	0.590
SBP before the epidural bolus	127.76 ± 24.74	131.28 ± 7.27	0.498
SBP after the epidural bolus	129.04 ± 5.83	127.60 ± 8.44	0.486
DBP before the epidural bolus	84.56 ± 4.70	82.80 ± 6.60	0.284
DBP after the epidural bolus	83.36 ± 4.57	80.64 ± 6.26	0.086
MAP before the epidural bolus	100.40 ± 4.010	99.20 ± 6.58	0.440
MAP after the epidural bolus	98.72 ± 4.20	96.60 ± 6.41	0.174
SPO2 (%) before the epidural bolus	99.28 ± 0.98	99.12 ± 0.88	0.547
SPO2 (%) after the epidural bolus	99.16 ± 1.06	98.92 ± 1.15	0.449

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Table 5: Mean haemodynamic and respiratory variables between two groups 1 minute before and 1 minute after epidural top-up

Haemodynamic and respiratory variables	Group A Mean ± S.D.	Group B Mean ± S.D.	P-value
HR before the epidural bolus	82.40 ± 7.416	82.28 ± 5.16	0.947
HR after the epidural bolus	80.96 ± 6.45	80.04 ± 5.39	0.587
SBP before the epidural bolus	130.96 ± 5.66	131.76 ± 5.39	0.671
SBP after the epidural bolus	129.36 ± 5.60	129.40 ± 7.05	0.982
DBP before the epidural bolus	85.12 ± 4.54	84.36 ± 5.36	0.591
DBP after the epidural bolus	84.16 ± 5.19	82.72 ± 5.192	0.332
MAP before the epidural bolus	100.20 ± 3.94	100.48 ± 5.56	0.838
MAP after the epidural bolus	99.16 ± 3.89	98.76 ± 5.35	0.764
SPO2 (%) before the epidural bolus	99.32 ± 0.74	99.08 ± 0.70	0.248
SPO2 (%) after the epidural bolus	99.44 ± 0.65	99.20 ± 0.81	0.256

No significant differences were found (Table/Fig 4 & 5) between the two groups in respect of haemodynamic and respiratory variables before and after epidural analgesia, (p>0.05).

Table 6: Mean duration of analgesia after epidural bolus and after epidural top-up

Group	After epidural bolus (hrs) Mean ± S.D.	After epidural top-up (hrs) Mean ± S.D.	P-value
Group A	(9.78 ± 1.73)	12.05 ± 1.83	0.001
Group B	(13.99 ± 0.95)	17.15 ± 1.11	0.001

The mean duration of analgesia of group B after epidural bolus and after epidural top-up was more prolonged than group A by 4.21 hrs and 5.10 hours (Table 6).

Table 7: Side-effects

Side-effects	Group A (n=25)		Group B (n=25)		P-value
	No. of patients	%	No. of patients	%	
Nausea	0	0	0	0	-
Vomiting	0	0	0	0	-
pruritus	2	8	1	4	P > 0.05
Bradycardia	0	0	0	0	-
Hypotension	0	0	0	0	-

DISCUSSION

The present study was conducted with the aim and objects to investigate whether there was any difference in the efficacy of postoperative epidural analgesia by a combination of morphine and bupivacaine and by plain morphine alone, to compare the haemodynamic and respiratory variables in the two groups during the study period and to evaluate and compare the post-operative side-effects in the two groups.

In this study, the demographic data [Table 2], pre-anaesthetic haemodynamic and respiratory variables [Table 3] between group A and group B were comparable and found statistically not significant (P> 0.05).

The mean duration of postoperative analgesia after administration of epidural bolus of morphine was 9.78 ± 1.73 hours. This is comparable to the study of Rawal N et el.[13] where the mean duration of postoperative analgesia was 10.7 ± 4.3 hours. The present finding is also comparable to the study of Yaddanapudi LN et al,[14] Parikh GP et al.[15]

In the present study, the mean duration of postoperative analgesia after administration of epidural bolus of 0.125% bupivacaine with 1 mg of morphine was 13.99 ± 0.95 hours. However, the mean duration of postoperative analgesia after the first epidural top-up was 8.4 ± 0.42 hours in Bhattacharyya R et al.[11] and 8.35 ± 0.42 hours in Parik TJ et al.[16] which is not comparable with the present study. This might be due to differences in body weight and body height which is lower in our study population. This might be also due to the ethnicity of the study population.[17,18]

The mean duration of postoperative analgesia of bupivacaine with morphine is longer than that of morphine by 4.2 hours after epidural bolus and 5.10 hours after epidural top-up. We have not been able to find other comparable similar studies to the present study with respect to the duration of postoperative analgesia after the administration of epidural morphine and epidural bupivacaine with morphine.

Morphine is a phenanthrene alkaloid of opium and is μ agonist that acts by decreasing the conductance of voltage-gated calcium channels or by opening the inward-flowing potassium channels.[19] which decreases neuronal activity. The local anaesthetic bupivacaine acts by blocking the voltage-gated sodium channels. These effects may contribute to synergism observed between local anaesthetics and opioids.[20] These synergistic effects may be the cause of the prolongation of postoperative analgesia in bupivacaine with morphine group.

The mean duration of postoperative analgesia in group A (morphine) is longer after epidural top-up than epidural bolus by 2.27 hours. Also, the mean duration of postoperative analgesia in group B (bupivacaine + morphine) is longer after epidural

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top-up than epidural bolus by 3.15 hours. The duration of postoperative analgesia is more marked with the second top-up of bupivacaine with morphine is consistent with a study done by Raghupatruni V et al.[20] This marked prolongation of the duration of postoperative analgesia with the second top-up has been attributed to the metabolites of morphine like morphine-6-glucuronide which is more potent and longer-acting than morphine.[20]

In the present study, no significant differences were found between the two groups in respect of haemodynamic and respiratory variables before and after epidural analgesia. This may be due to the usage of low doses of bupivacaine and morphine in our study.

No side effects were observed except the incidence of pruritus seen in two patients (8%) receiving epidural morphine and one patient (4%) receiving epidural bupivacaine with morphine [Table 7].

Limitation

In the present study, the dose of the study drugs was fixed irrespective of the body weight and height of the study population. Secondly, the ethnicity of the study population was not maintained. The study may be more significant if the dose of the study drugs is given by calculating based on the body weight of the participants with the same ethnicity.

CONCLUSION

Use of bupivacaine (0.125%) 8 ml with 2 ml of injection morphine (1mg) given epidurally provides better postoperative analgesia with a longer duration of analgesia than 10 ml of 1 mg morphine epidurally in adults for lower limb orthopaedic surgery with a minimal manageable side effect.

Conflict of Interest Nil

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