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Intraperitoneal Bupivacaine 0.25% versus intravenous Diclofenac on post-operative analgesia in the cesarean section under spinal anesthesia: A prospective randomized comparative study in a tertiary care hospital of India

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ABSTRACT

Background: Cesarean section (CS) is a common surgical procedure, often accompanied by significant post-operative pain, which can hinder recovery, bonding with the baby, and breastfeeding. Effective pain management is crucial to prevent complications such as chronic pain and depression. Intraperitoneal (IP) instillation of local anesthetics, such as Bupivacaine has shown promise in providing analgesia, while intravenous (IV) Diclofenac is a common alternative. **Aims and Objectives:** This study aimed to compare the post-operative analgesic efficacy of IP Bupivacaine with IV Diclofenac in parturients undergoing lower segment CS (LSCS). **Materials and Methods:** A randomized, double-blind, prospective study was conducted in Deen Dayal Upadhyay Hospital, New Delhi, with 60 patients divided into two groups: Group B received IP Bupivacaine (30 mL, 0.25%) and Group D received IV Diclofenac (1 mg/kg). Post-operative pain was assessed using the Visual Analog Scale (VAS) at various time points up to 24 h. The time to first rescue analgesia and total analgesic requirement were also measured. **Results:** Group B had significantly lower VAS scores at 6, 8, 10, 12, and 24 h post-operatively ($P<0.05$). Time to first rescue analgesia was longer in Group B (7.26 ± 1.04 h) compared to Group D (5.01 ± 0.49 h) ($P=0.001$), and the total analgesic requirement was lower in Group B ($P=0.01$). Early breastfeeding was more feasible in Group B. **Conclusion:** IP Bupivacaine provided superior analgesia compared to IV Diclofenac, promoting earlier mobilization, bonding, and breastfeeding. It is a simpler and more effective method for post-operative pain management in LSCS.

Key words: Cesarean section; Post-operative pain; Bupivacaine; Local analgesia; Pain measurement

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INTRODUCTION

Delivery by cesarean section (CS) is becoming more frequent and is one of the most common major operative procedures performed worldwide. In the United States of America, a CS rate of 26% for all births is reported.[1] The rate approaches 25% in Canada and is over 20% in England, Wales and Northern Ireland.[2]

Childbirth is an emotional experience for a woman and her family too. CS is the most common surgery which is performed worldwide and delivery by CS is becoming

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more frequent. It is estimated that 33% prevalence is there of CS in India. Pain is ranked highest among undesirable outcomes associated with CS.[3] Acute pain following delivery imparts a significant risk factor for persistent pain and depression. Such an observation outlines a need to more carefully address pain management in the days following childbirth.[4] As the mother needs to bond with the new baby as early as possible and initiate breastfeeding, which helps to contract the uterus and accelerates the process of uterine involution in the postpartum period. Effective treatment of post-operative pain contributes to decreasing the rate of complications, such as emotional and physical suffering, overt use of opioids, sleep disturbance, cardiovascular side effects, increased oxygen consumption as well as the total cost of the operated patients and development of chronic post-surgical pain. Post-CS pain complicates the post-operative recovery in women.[5]

CS is performed under spinal anesthesia, spinal epidural, epidural block, or general anesthesia. Short- or medium-acting sedatives, narcotics, and local anesthesia have been employed during the operation as an adjunct to anesthesia or to alleviate post-operative pain. Local anesthetics cause reversible blockade of impulse propagation along the nerve fibers by preventing the influx of sodium ions through the cell membrane of the fibers.

The fact that the pain comprises several components accounts for the necessity of multimodal analgesia techniques to provide effective post-operative analgesia.[6] Intraperitoneal (IP) instillation of local anesthetic has been promising to minimize post-operative pain. The local anesthetic inhibits nociception by affecting nerve membrane-associated proteins and by inhibiting the release of prostaglandins and other agents that sensitize or stimulate the nociceptors and contributes to inflammation. Instillation of IP local anesthetics lignocaine, Bupivacaine, levobupivacaine, and ropivacaine have been used following laparoscopic gynecological and general surgical procedures to reduce pain through randomized trials for many years.[7-10]

Bupivacaine blocks the generation as well as the conduction of nerve impulses by enhancing the electrical excitation threshold, slowing the propagation of the nerve impulse, and decreasing the rate of increase of the action potential. It also inhibits depolarization by binding to the intracellular portion of Na channels and blocking Na+ influx into neurons. Usually, the progress of anesthesia is associated with the diameter, myelination, and conduction velocity of affected nerve fibers. The order of loss of nerve function is pain, temperature, touch, proprioception, and skeletal muscle tone. Its analgesic effects are because of its binding to the prostaglandin E2 receptors, subtype EP1; this leads to inhibition of prostaglandins production, and thus decreases fever, inflammation, and hyperalgesia.[11]

Diclofenac on the other hand is a proven non-steroidal anti-inflammatory drug that exerts its action by inhibiting cyclooxygenase-1and cyclooxygenase-2 with relative equipotency.[12]

Aims and objectives

The primary objective of the present study was to evaluate the post-operative analgesic efficacy of intra-peritoneal instillation of Bupivacaine as compared to intravenous Diclofenac sodium in parturient undergoing lower segment caesarean section (LSCS). The other objectives were decided secondarily to compare the time for first rescue analgesia, the total rescue analgesic requirement upto 24 hours post-surgery, the adverse effects and the time to first breast feeding.

MATERIALS AND METHODS

This was a prospective randomized comparative double-blind study conducted in the Department of Anesthesiology and Critical Care, Deen Dayal Upadhyay Hospital, Hari Nagar, New Delhi for a period of 1 year after obtaining approval from the ethical committee of the institution (IEC-DDUH/upn59/2021–03–23/59/v1) and written informed consent of study participants.

Inclusion criteria

Parturient coming to Deen Dayal Upadhyay Hospital, Hari Nagar, New Delhi for delivery satisfying pre-fixed criteria such as undergoing lower segment CS at full term under spinal anesthesia, ASA grade II (normal pregnancy without any comorbidity), weight recorded in first ANC ≥50 kg, age 18–35 years, height ≥5 feet (152.4 cm), and without any fetal distress, were included in the study.

Exclusion criteria

Patients with a history of allergies to the study drug, ASA grade III and above, undergoing LSCS has done under GA, any history of coagulopathy, and any contraindication to spinal anesthesia were excluded.

The sample size was calculated taking the result of the study of Pareek et al.,[13] which observed that mean Visual Analog Scale (VAS) at 2 h in Bupivacaine (0.25%) was 2.6±1.94. Taking these values as a reference and assuming a difference of 1.5, the minimum required sample size with 80% power of the study and 5% level of significance was 27 patients in each study group using the formula for comparative study by comparing means of two independent groups (n=2 [standard deviation]^2 *[$Z\alpha+Z\beta$]/[mean difference]^2, where $Z\alpha$ is the value of Z at two-sided alpha error of 5% and Z_β is the

value of Z at the power of 80% and the mean difference is a difference in mean values of two groups). To reduce the margin of error, the total sample size was finalized as 60 (30 patients per group) taking the loss to follow-up as 10%.

Randomization technique

Variable block randomization with a sealed envelope system was done. In this, the total sample was divided into a variable number of blocks each containing an even number of sealed envelopes. In each block, assigning B and D, having equal numbers in each group, where B represented the group receiving IP Bupivacaine, and D represented the group receiving IV Diclofenac.

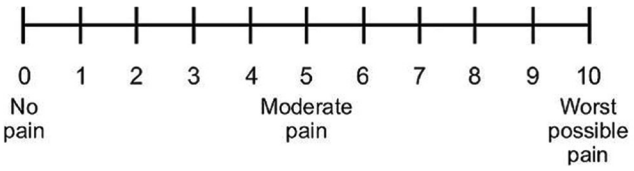
Once a patient gave consent to enter the trial, the patient was asked to pick up one sealed envelope from one block, and she was offered the allocated group. In this technique, patients were randomized in a series of blocks of variable numbers that were for every certain group of patients (such as 8, 10, and 12, randomized as 4, 5, 6, etc.) who received IP Bupivacaine, and other same number received injection Diclofenac.

This randomization was done with the help of a computer, and after that, patients were allocated to one of the two study groups as Group B where patients were given IP instillation of 30 mL, 0.25% Bupivacaine, and Group D where patients were given intravenous Diclofenac.

Blinding

The study was conducted in a double-blinded fashion through sealed envelope system where both the parturient and the principal investigator were not aware of the study group. The drugs for the study group were prepared and administered by the anesthesiologist not involved in the study.

Bupivacaine 0.5% 30 mL vial, Diclofenac sodium 1ml ampoule, anesthesia workstation and monitors (electrocardiogram, non-invasive blood pressure, Pulse Oximeter), disposable syringes and needles, gloves, intravenous cannulas, anesthesia machine and trolley with all emergency drugs and instruments, intravenous fluids such as colloids/crystalloids, Cetrimide-chlorhexidine gluconate solution, povidone-iodine solution, isopropyl alcohol, sterile gown and sterile gloves, a sterile tray containing sterile sponge holder, gauge pieces, syringes, needles, and drape sheet, 25G Quincke spinal needle, injection Bupivacaine hydrochloride 0.5% (Heavy) 4 mL, injection Atropine sulfate, and injection Mephentermine were used as the materials for the conduction of the study, and on the other hand, VAS for global abdominal pain was used as the tool to monitor the post-operative pain. The VAS, a pain-rating scale, was used by Hayes and Patterson in 1921 for the 1st time.[14] VAS Scoring is performed on the basis of self-reported measures of symptoms, which shows a continuum between the two ends of the scale: "No pain" on the left end (0 cm) of the scale and the "worst pain" on the right end of the scale (10 cm). Measurements from the starting point (left end) of the scale to the patients' marks are recorded in centimeters and are interpreted as their pain. These values are used for tracking the progression in pain for a patient or for comparing pain among patients who have the same conditions. This scale can also be used for assessing appetite, dyspepsia, mood, severity of asthma, and ambulation are recorded with a single handwritten mark placed at one point along the length of a 10-cm line.[15]



Visual analog scale

All patients had undergone pre-anesthetic evaluation that included detailed history, examination, and relevant investigations. Patients were explained about the method of pain assessment using VAS. Patients scheduled for elective surgery were advised to fast overnight and receive tablet Ranitidine (150 mg) and tablet Metoclopramide (10 mg) the night before surgery and 2 h pre-operatively. The fasting status of the patients scheduled for emergency cesarean delivery was noted, and they received injection Ranitidine 150 mg IV and Metoclopramide 10 mg IV for gastric aspiration prophylaxis.

Baseline readings of heart rate, blood pressure (systolic, diastolic, and mean), and oxygen saturation were noted. Vascular access was secured using an 18-gauge intravenous cannula. Under all aseptic pre-cautions, CS was carried out under spinal anesthesia with a 25 Gauge Spinal needle using 2.5 mL of hyperbaric injection Bupivacaine hydrochloride 0.5%.

Each patient was randomly assigned to one of the two groups of 30 patients each using a sealed envelope system. Group B received 30 mL of 0.25% Bupivacaine intraperitoneally after visceral peritoneal closure and attaining complete hemostasis and evacuation of pelvic pooled blood ensuring instillation on the uterine stitch line, pelvis, and surrounding area, whereas group D received Diclofenac sodium injection intravenously at a dose of 1 mg/kg after skin closure. All the study drugs were prepared, coded, and instilled by an anesthesiologist. Any intraoperative complication such as hemodynamic instability or fetal compromise was noted. The outcome was measured by assessing the post-operative

pain at 0 h (at the end of surgery in the post-operative room) and subsequently at 2, 6, 12, and 24 h by the VAS scoring system for global abdominal pain. Duration of analgesia was calculated based on time to first rescue analgesia (injection Diclofenac Sodium −1 mg/kg) which was given as soon as VAS ≥3 as VAS <3 means analgesia is adequate. The total analgesic requirement for 24 h was recorded. The time to first breastfeed was also recorded. Any adverse events such as (Hypotension, Bradycardia, Nausea and Vomiting, Dizziness, Paresthesia [Tingling Sensations and Numbness], and headache) within 24 h post-operatively were recorded.

The data were analyzed using Statistical Package for Social Sciences version 21.0 after entering it in MS EXCEL spreadsheet. A P=0.05 was considered to be statistically significant. Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean±SD and median. The normality of data was tested by the Kolmogorov–Smirnov test. Non-parametric test was used for not normally distributed data. For quantitative variables, the unpaired t-test or Mann–Whitney test between the two groups, and for qualitative variables, the Chi-square test/Fisher's exact test was applied.

RESULTS

The mean age, height, and weight of the parturient in Group B was (24.63±3.5), (155.50±2.1), and (64.6±3.3), respectively, whereas for Group D, it was (25.73±3.9), (154.57±2.2), and (62.07±5.1), respectively, which were found to be comparable on statistical analysis P=0.25, 0.1, and 0.02, respectively (Table 1).

In this study, the mean VAS score readings at 0 h for Group B was 0.30±0.7 and for Group D was 0.17±0.5, (P=0.36). With the progression of time, VAS score were lower in Group B as compared to Group D and the readings were, at 2 h-1.13±0.8, 1.20±0.714 (P=0.73); at 6 h-1.20±0.9, 1.40±0.6 (P=0.02); at 8 h-0.83±0.9, 1.97±0.6 (P=0.01); at 10 h-1.30±0.6, 2.47±0.9 (P=0.001); at 12 h-1.43±1.5, 2.90±0.9, (P=0.001) and at 24 h-0.93±0.8, 1.23±0.1 (P=0.001), respectively. The mean VAS score at 0 h was found to be statistically insignificant; however, the mean VAS score readings were statistically significant at 6, 8, 10, 12, and 24 h (Figure 1).

Mean Time to first rescue analgesia was more with Group B (7.26±1.04) as compared to Group D (5.01±0.49) and was found to be statistically significant with P=0.001. The total analgesia required was significantly less with Group B (130±39.1) as compared to Group D (160±51.1) (P=0.01). Group B (1.24±0.1) mother could breastfeed her baby earlier as compared to Group D (1.33±0.1) which was also found to be statistically significant (P=0.001) (Table 2).

Adverse effects such as Nausea and vomiting were seen in a few parturients of Groups B and D which were statistically insignificant (P>0.05) (Table 3).

Table 1: Baseline demographic statistics of study participants

Demographic characteristics	Group B (n1=30)	Group D (n2=30)	P-value
	Mean (±SD)	Mean (±SD)	
Age (years)	24.63 (±3.5)	25.73 (±3.9)	0.25
Height (cm)	155.5 (±2.1)	154.57 (±2.2)	0.1
Weight (kg)	64.6 (±3.3)	62.07 (±5.1)	0.02

Table 2: Comparison between time for first rescue analgesia, total analgesia required and time to first breastfeed

Variables	Group B (n1=30)	Group D (n2=30)	P-value
	Mean (±SD)	Mean (±SD)	
Time for first rescue analgesia (h)	7.26 (±1.04)	5.01 (±0.49)	0.001
Total analgesia required (mg)	130 (±39.1)	160 (±51.1)	0.01
Time to first breastfeed (h)	1.24 (±0.1)	1.33 (±0.1)	0.001

Table 3: Comparative frequency of post-operative adverse effects

Adverse effects	Group B (n1=30)	Group D (n2=30)	Chi-square value (df)	P-value
	No (%)	No (%)		
Nausea	1 (3.3)	2 (6.7)	2.289 (2)	0.32
Vomiting	0 (0)	2 (6.7)		
Nil	29 (96.7)	26 (86.7)		

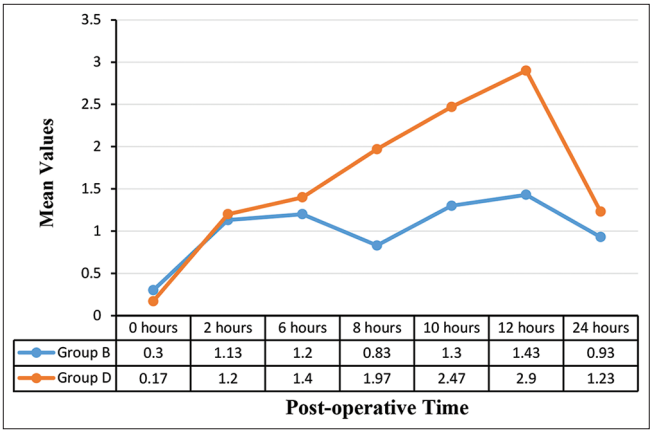


Figure 1: Trend of mean post-operative VAS score with progression of post-operative time

No incidence of hypotension, arrhythmias, or respiratory depression was noted in any group.

DISCUSSION

The present study was a prospective randomized comparative double-blind trial on 60 parturients where a comparison in the use of Bupivacaine (Group B, n1=30) and systemic analgesic Diclofenac (Group D, n2=30) for determining post-operative analgesia in women undergoing CS was done. The statistical analysis of both the groups regarding demographic data and baseline hemodynamic parameters among the two study groups were found to be comparable.

The mean age of the parturient in Groups B and D in this study were comparable to the study by Pareek et al.,[13] and Sharan et al.,[16] Malhotra et al.[17] A similar age group has been reported in those studies conducted on this subgroup of the population.

In this study, similarity in height and weight ensured the equivalent distribution and action of anesthesia among the study population. Even other studies ensure comparable height and weight as reported by Sharan et al.,[16] and Malhotra et al.[17] In this study, all patients belonged to ASA grade II in all the two groups.

The hemodynamic parameters at 0 h, 2 h, 6 h, 8 h, 10 h, 12 h, and 24 h were found to be comparable in both the groups which is similar to the findings of the study of Pareek et al.[13] Babu et al.,[18] in a similar study design, reported that the vital parameters were similar among the groups.

The analgesic effect of the two study drugs was compared by the VAS scoring system. The mean VAS score readings at 0 h among the two groups were statistically insignificant. However, with the progression of post-operative time, the mean VAS score readings were lower in the Bupivacaine group in comparison with the Diclofenac group and were statistically significant at 6, 8, 10, 12, and 24 h. Devalkar and Salgaonkar[19] noted that the mean VAS score readings were lower in the Bupivacaine group in comparison with the normal saline group and were statistically significant at 2, 4, 8, and 12 h. Similarly, Malhotra et al.,[17] observed that in the Bupivacaine group, VAS scores were significantly lower at 2 and 4 h than in control groups. However, the VAS score was comparable at 6 and 8 h following surgery.

Thus it is seen that although both the study drugs are efficacious as per their individual mechanism of action, Bupivacaine provided better analgesia (as reflected by the VAS score) than Diclofenac.

Time to first rescue analgesia was corroborated with a VAS score ≥3. Mean time for first rescue analgesia was longer in Group B compared to Group D. The total analgesic requirement in 24 h was significantly less with Group B as compared to Group D. These findings are consistent with the study by Pareek et al.,[13] who reported that the analgesic effect was more pronounced in Bupivacaine group on comparing time to first analgesic requirement, the mean of duration of analgesia in Group B (Bupivacaine) was higher as compared to Group C (control), during the post-operative period. The difference was statistically and clinically significant. The total analgesic requirement was significantly less in Group B than in Group C. This indicates that Bupivacaine provided longer duration and denser analgesia as compared to the control group. Although as per their study, Ropivacaine provided the best results. Similar findings had also been reported in Sharan et al.,[16] Narchi et al.,[20] and Kucuk et al.[10]

It had been also observed in this study that in Group B, mothers could breastfeed their baby much earlier as compared to Group D. All the patients of both the groups were able to breastfeed before 2 h but the mothers of Group B could breastfeed their baby on an average at 1 h and 20 min which was strongly significant. We could not find any study that compared the time to first breastfeed receiving a similar sort of analgesia but it is necessary to mention that in a study conducted by Chang and Heaman,[21] women who received no analgesia were compared to those who received continuous epidural analgesia with fentanyl and ropivacaine or Bupivacaine during labor and delivery. However, the study was inconclusive with no observation during the initial 1–2 post-operative hours. Delayed bonding with the baby and delayed breastfeeding makes CS delivery disadvantageous over normal vaginal delivery. This study reflected about the bridging of this gap as IP instillation of Bupivacaine (Group B) allowed the mothers to breastfeed the babies much earlier than the mothers who received the usual institutional protocol of Intravenous Diclofenac (Group D).

Some mild post-operative complications such as nausea and vomiting were noted in some parturient of both groups, but no incidence of hypotension, arrhythmias, or respiratory depression was noted in any group. It indicates that IP instillation of Bupivacaine as well as intravenous Diclofenac in the volume and dose used in the study was not associated with any significant adverse effects. This is supported by the findings of the study by Pareek et al.,[13] who reported that complications were noted in only <10% of the patients in group B. Nausea was noted in two patients in group B. Similar findings were reported by Sharan et al.,[16] and Malhotra et al.[17]

Strengths of the study

A comparatively easier means of providing post-operative analgesia after CS in the form of IP instillation of local anesthetic is being studied. The study being randomized, comparative trial holds statistical strength and thus its results shall be helpful in understanding the efficacy of Bupivacaine particularly in CS. This is probably the first in this kind of trial where the effect of IP instillation of local anesthetic and intravenous Diclofenac after CS on time to first breastfeed has been evaluated.

Limitations of the study

Although the sample size of this study had a power of 80%, to establish the efficacy of the post-operative analgesic effect of IP instillation of Bupivacaine, a larger sample size, and a multi-centric trial is needed to gain more information about the efficacy. Here, in this study parturients with ASA >2 were not included; hence, the efficacy of the technique in parturients with co-morbidities will need further evaluation. The study was limited only to CS wherein only the lower abdomen was involved. Various other doses of Bupivacaine were also not within the scope of this study.

CONCLUSION

The study concludes that IP instillation of Bupivacaine is a much easier and simpler means of providing post-operative pain relief in lower segment CS. The quality of analgesia is good, in terms of patient satisfaction, early mobilization, early bonding with the neonate, and early breastfeeding. The requirement of systemic analgesics in the first 24 h is considerably reduced with IP instillation of Bupivacaine as compared to intravenous Diclofenac. On comparison, local instillation of Bupivacaine has given better results than the usual practice of systemic use of Diclofenac. Hence, it can be recommended as a simpler method of post-operative analgesia in CS.

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Authors Contribution:
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