Original Article

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Anaesthesia Section

Intrathecal Buprenorphine versus Intrathecal Fentanyl as Adjuvants to Hyperbaric Bupivacaine in Spinal Anaesthesia for Lower Segment Caesarean Sections: A Randomised Clinical Study

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ABSTRACT

Introduction: Spinal anaesthesia is the choice technique for Lower Segment Caesarean Section (LSCS). When using subarachnoid block (spinal analgesia), opioids are employed as the main adjuvants along with local anaesthetics to achieve intra/postoperative analgesia. These opioids have desirable properties such as reducing the dose of local anaesthetics, minimising side-effects, providing analgesia, and prolonging the duration of anaesthesia.

Aim: To evaluate and compare the efficacy between intrathecal Buprenorphine and Fentanyl as adjuvants to hyperbaric bupivacaine (0.5%) in women undergoing LSCS under spinal anaesthesia.

Materials and Methods: A randomised double-blinded clinical trial was conducted at Bharati Vidyapeeth Hospital and Research Centre in Pune, Maharashtra, India between July 2021 and February 2022. A total of 80 parturients with American Society of Anaesthesiologists (ASA) grade II, aged 18 and older, scheduled for elective LSCS, were randomly divided into two groups of 40 each. Group B received 1.8 mL of 0.5% Bupivacaine with 60 µg Buprenorphine, while Group F received 1.8 mL of 0.5% Bupivacaine with 25 µg Fentanyl. The onset/duration of motor block and sensory block, intraoperative haemodynamics, side-effects, postoperative pain, and demand for the first rescue analgesia were assessed using Chi-square test, Fisher's-exact probability test, or independent sample t-test.

Results: Demographic data such as age, weight, Body Mass Index (BMI), and ASA grade were similar in both groups. The mean duration of surgery in Group B and Group F was 48.12±6.86 min and 48.25±6.56 min, respectively. The mean duration of sensory blockade in Group B was 264.38±37.16 min, and in Group F it was 193.50±34.27 min. The total duration of motor block was 231.00±43.74 minutes in Group B and 171.00±36.87 min in Group F. The total duration of sensory and motor block in Group B was significantly longer (p-value <0.05). The mean time to first rescue analgesia in Group B and Group F was 304.63 min and 228.63 min, respectively (p-value <0.05).

Conclusion: The present study concluded that both drugs are safe and suitable as adjuvants with local anaesthetics in spinal anaesthesia for LSCS. The addition of intrathecal buprenorphine to bupivacaine provides a more promising postoperative analgesic effect compared to intrathecal fentanyl, without causing any significant maternal or neonatal side-effects.

Keywords: Haemodynamics, Local anaesthetics, Spinal analgesia, Sensory block

INTRODUCTION

Generally, postoperative analgesia after LSCS is often inadequate due to a misunderstanding of maternal and neonatal side-effects [1]. Spinal Anaesthesia (SAB) is commonly preferred for LSCS due to its rapid onset of action, minimal intraoperative haemodynamic changes, gradual resolution of analgesia during recovery, lower maternal mortality/morbidity rates, and reduced risk of failed intubation and aspiration pneumonitis [2].

The administration of intrathecal opioids remains the gold standard for postoperative analgesia [3]. The first published report on intrathecal opioids for anaesthesia dates back to Rocoviceanu-pitesti in 1901 [4]. Buprenorphine, a thebaine derivative agonist-antagonist opioid, has an affinity for µ receptors that is 50 times greater than morphine. Fentanyl, a synthetic opioid belonging to the phenylpiperidine group, is 75 to 125 times more potent than equivalent doses of morphine [5]. The transfer of opioids via epidural or parenteral routes results in higher placental/neonatal drug transfer compared to the relatively smaller transfer in subarachnoid blocks [6].

Abate SM et al., conducted a meta-analysis on the efficacy of low-dose bupivacaine with different doses of intrathecal fentanyl in LSCS and found that fentanyl in the range of 10-25 µg provides stable haemodynamics and adequate analgesia without significant maternal and foetal side-effects [7]. Thatipamula N et al., performed a comparative study with intrathecal hyperbaric bupivacaine using varying doses of buprenorphine for LSCS. They found that increasing the dose from 45 mcg to 60 mcg did not exacerbate side-effects in the mother and foetus but significantly improved analgesic efficacy [8].

There is limited literature available directly comparing smaller doses of buprenorphine versus fentanyl exclusively in parturient women. With this background, the present study aims to evaluate and compare the efficacy of intrathecal buprenorphine and fentanyl as adjuvants to heavy bupivacaine (0.5%) in women undergoing LSCS under spinal anaesthesia [8,9].

MATERIALS AND METHODS

This was a randomised double-blinded clinical trial conducted at Bharati Vidyapeeth Hospital and Research Centre in Pune, Maharashtra, India, between July 2021 and February 2022. The study received approval from the Institutional Ethics Committee (BVDUMC/IEC/72) and was registered as a clinical trial (CTRI/2021/07/034806).

The primary outcome of the study was the onset and duration of sensory and motor blockade, as well as intraoperative/postoperative analgesia. The secondary outcomes included intraoperative/postoperative haemodynamic monitoring, side-effects, and complications.

Sample size calculation: The sample size for the study was calculated based on a previous article by Sittaramane S and Dhakshunamoorty [9]. The formula used for sample size calculation was: $n=(Z_{\alpha/2}+Z\beta)^2*2*\sigma^2/d^2$, where:

- $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$
- $Z\beta$ is the critical value of the Normal distribution at β
- σ^2 is the population variance
- d is the desired difference to detect

Inclusion criteria:

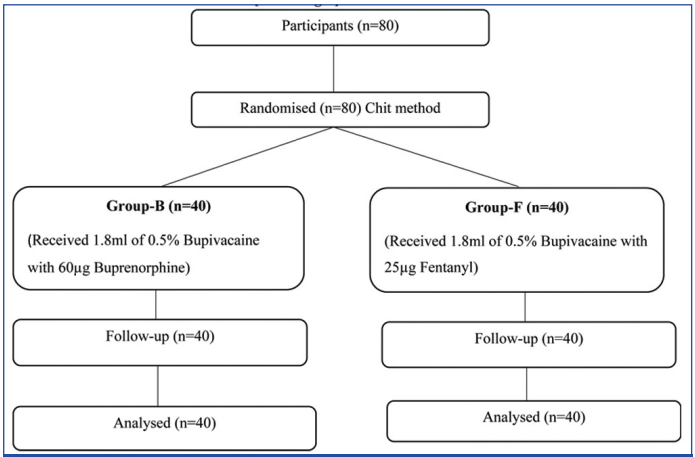
- ASA II patients
- Patients aged 18 years and above

Exclusion criteria:

- Patients unwilling to undergo spinal anaesthesia
- ASA III, IV, V patients.
- Patients with co-morbidities during pregnancy, such as gestational diabetes mellitus, pregnancy-induced hypertension, and heart disease
- Patients with contraindications for spinal anaesthesia

Study Procedure

A total of 80 patients meeting the inclusion/exclusion criteria were randomly selected using a chit system and divided into two groups [Table/Fig-1]: Group B received 1.8 mL of 0.5% Bupivacaine with 60 µg Buprenorphine, and Group F received 1.8 mL of 0.5% Bupivacaine with 25 µg Fentanyl [9].



[Table/Fig-1]: Consolidated standards of reporting trials (CONSORT) data.

A detailed preanaesthetic checkup was conducted one day before surgery. Baseline vitals, body weight, and height were recorded, and the procedure and Visual Analogue Scale (VAS) chart were explained to the patients.

After confirming that the patients were nil by mouth, they were taken to the operation theatre. Standard monitors, including a three-lead electrocardiograph, non invasive blood pressure cuff, and pulse oximeter, were attached, and baseline vitals were noted. Preloading was done with 500 mL of Ringer's lactate solution.

The study drugs were prepared by an anaesthesiologist who was not involved in patient care. Both the parturient and the attending anaesthesiologist were unaware of the study drug solution. Under aseptic conditions, the patients were placed in a sitting position, and spinal anaesthesia was performed using a 25 G Quincke spinal needle in the L2-L3/L3-L4 intervertebral space with a midline approach. After confirming dural puncture by aspiration of cerebrospinal fluid, the drug was injected into the subarachnoid space over 10 to 15 seconds.

After the subarachnoid spinal anaesthetic injection, the patient was positioned supine with left uterine displacement or with a wedge under 2 the right hip and a pillow under the shoulder, creating a 30° angle with the bed.

The evaluation included noting the time of drug injection. The level of sensory block was assessed using the pin prick method in the midclavicular line. The onset time was defined as the time from drug injection into the intrathecal space to the achievement of the T10 dermatomal level. Once the sensory block reached the T6 level, surgical incision was allowed.

Motor block was assessed using the Modified Bromage Scale. Motor block assessment continued until the maximum block was achieved (Bromage score of 3) [10].

Cardiorespiratory parameters such as Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Heart Rate (HR) were monitored at five-minute intervals for the first 10 minutes and then every 10 minutes for the remainder of the surgical procedure. Intraoperatively, an SBP less than 90 mmHg or a decrease of more than 20% from the baseline was treated with an intravenous fluid bolus and 6 mg of intravenous Ephedrine. Bradycardia (HR less than 60 per minute) was treated with 0.64 mg of intravenous Atropine or 0.2 mg of intravenous Glycopyrrolate. A respiratory rate of less than 10 per minute was considered respiratory depression, and if any signs of respiratory depression or SpO_2 dropping below 95% were observed, treatment involved using a Hudson mask with 6 to 8 litres per minute of oxygen.

If the sensory block failed to reach the T6 level within 10 minutes of performing the subarachnoid spinal block, a 10° head-down tilt was applied. Twenty units of intravenous oxytocin were administered after the delivery of the baby and clamping of the umbilical cord.

Regression of sensory block was determined as the time for a two-segment regression from the maximum achieved sensory dermatome level. Postoperatively, pain was assessed using a standard 10 cm linear VAS every hour for the first six hours. The duration of analgesia was defined as the interval between the injection of the intrathecal drug and the time of the first demand for rescue analgesia. Rescue analgesia was provided as 1 gram of intravenous Paracetamol when the VAS score reached 3 or higher.

Patients were also evaluated for the duration of motor block, sensory block, and side-effects such as nausea, pruritus, respiratory depression, foetal Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score, and Ramsay Sedation Score.

STATISTICAL ANALYSIS

The intergroup comparison of categorical variables is tested using the Chi-square test or Fischer's-exact probability test, while normally distributed continuous variables are tested using the independent sample t-test. In the entire study, p-values less than 0.05 are considered statistically significant. The entire data is statistically analysed using the Statistical Package for Social Sciences (SPSS, version 22.0, IBM Corporation, USA) for MS Windows.

RESULTS

Demographic data such as age, weight, body mass index, ASA grade, and total duration of surgery were similar in both groups [Table/Fig-2].

Demographic data	Group B (n=40) Mean±SD	Group F (n=40) Mean±SD	p-value
Age (years)	28.42±4.52	28.08±5.22	0.750
Body weight (kg)	64.98±8.12	66.63±8.96	0.391
BMI (kg/m^2)	24.91±3.02	25.65±3.42	0.310
Duration of surgery (min)	48.12±6.86	48.25±6.56	0.934

[Table/Fig-2]: Comparison of Demographic distribution.
Values are mean and Standard Deviation (SD), p-value by independent sample t-test. p-value >0.05 is considered to be statistically non significant

The mean onset of sensory block in Group B and Group F was 156.63 seconds and 187.75 seconds, respectively. The minimum-maximum time range in Group B and Group F was 60-360 seconds and 60-450 seconds, respectively, which was statistically non-significant (p-value >0.05).

The mean time for the maximum sensory block in Group B and Group F was 309.75 seconds and 339.13 seconds, respectively. The minimum-maximum time range in Group B and Group F was 180-450 seconds and 120-600 seconds, respectively. The mean time for the maximum sensory block did not differ significantly between the two study groups (p-value >0.05). The mean onset of bupivacaine-induced sensory block was not affected by any of the opioid adjuvants.

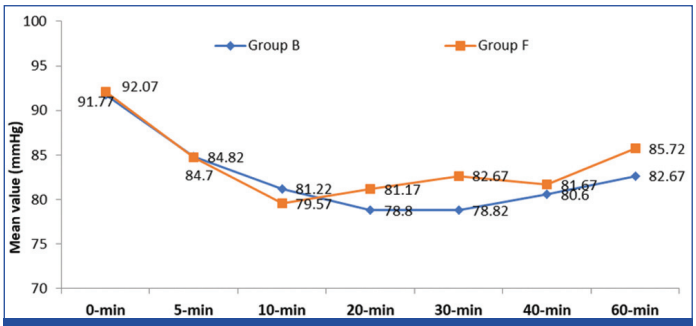
The mean onset of motor block in Group B and Group F was 134.25±61.51 seconds and 158.87±70.90 seconds, respectively. The minimum-maximum time range in Group B and Group F was 60-300 seconds and 60-360 seconds, respectively. The mean time for the onset of motor block did not differ significantly between the two study groups (p-value >0.05).

The mean time for peak motor block in Group B and Group F was 222.00±66.49 seconds and 259.25±80.01 seconds, respectively [Table/Fig-3]. The minimum-maximum time range in Group B and Group F was 120-360 seconds and 120-480 seconds, respectively. The mean time for complete motor block is significantly longer in Group F compared to Group B (p-value <0.05). This indicates that the addition of buprenorphine enhances the completion time for motor blockade.

Time	Group B (n=40) Mean±SD	Group F (n=40) Mean±SD	p-value
Time for peak motor block (sec)	222.00±66.49	259.25±80.01	0.026*

[Table/Fig-3]: Intergroup comparison of mean time for peak motor block.
Values are mean and SD, p-value by independent sample t-test. p-value <0.05 is considered to be statistically significant. *p-value <0.05

The distribution of mean HR, SBP, DBP, mean arterial blood pressure at 0 min, 5 min, 10 min, 20 min, 30 min, 40 min, and 60 min among the cases studied did not differ significantly between the two study groups (p-value >0.05) [Table/Fig-4].



[Table/Fig-4]: Intergroup distribution of mean MAP.

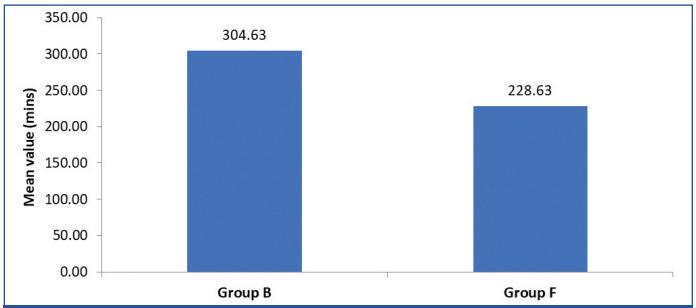
The incidence of intraoperative hypotension was noted in 5 out of 40 patients in Group F and 3 out of 40 patients in Group B. There was no evidence of respiratory depression in either group. The distribution of intraoperative complications such as vomiting, respiratory depression, and hypotension among the cases studied did not differ significantly between the two study groups (p-value >0.05 for all).

The distribution of mean Ramsay Sedation scale intraoperative and at 0 hr, 1 hr, 2 hr, 3 hr, 4 hr, and 5 hr among the cases studied did not differ significantly between the two study groups (p-value >0.05 for all). The distribution of mean APGAR score (1-min and 5-min) among the cases studied did not show any incidents of foetal hypoxia. It did not differ significantly between the two study groups (p-value >0.05). When comparing the mean regression time for sensory and motor block, patients in Group B showed a significantly longer duration compared to those in Group F (p-value <0.05). This indicates a significantly longer time of continued sensory and motor blockade in Group B than in Group F [Table/Fig-5].

Time (min)	Group B (n=40) Mean±SD	Group F (n=40) Mean±SD	p-value
Regression of sensory block	264.38±37.16	193.50±34.27	0.001***
Regression of motor block	231.00±43.74	171.00±36.87	0.001***

[Table/Fig-5]: Intergroup comparison of mean regression of sensory and motor block.
Values are mean and SD, p-value by independent sample t-test. p-value <0.05 is considered to be statistically significant. *p-value <0.05

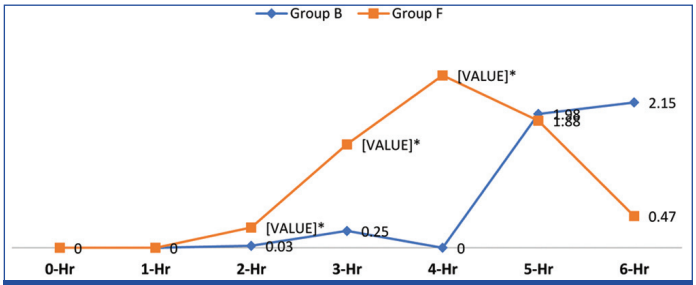
The requirement for the first rescue analgesia time showed that the mean first rescue analgesia time in Group B was 304.63 minutes (range 195-360 min), while in Group F it was 228.63 min (range 160-300 min). This confirms that the effective block wore off earlier in Group F, resulting in a quicker requirement for first rescue analgesia compared to Group B (p<0.05) [Table/Fig-6].



[Table/Fig-6]: Intergroup distribution of mean time to first rescue analgesia.

The distribution of mean pain score (VAS) at 2 hr, 3 hr, and 4 hr suggested that the pain score was much lower and better controlled in Group B compared to Group F, where the VAS scores were much higher (p<0.05).

[Table/Fig-7] shows that the mean pain scores (VAS) were much higher at six hours duration in patients receiving fentanyl compared to those receiving buprenorphine, indicating a much shorter duration of fentanyl compared to buprenorphine.



[Table/Fig-7]: Intergroup distribution of mean pain score (VAS).

DISCUSSION

The mean regression time of sensory block in Group B was 264.38 minutes, and in Group F it was 193.50 minutes. The mean regression time of motor block in Group B was 231 minutes, and in Group F it was 171 minutes. In this study, the mean regression time for sensory and motor block among the cases studied is significantly longer in Group B compared to Group F (p-value <0.05) [Table/Fig-3]. This shows a significantly longer time of continued sensory and motor blockade in Group B than in Group F.

Pathak DB and Engti P, in their study, found that the mean duration of sensory and motor blockade produced by buprenorphine was longer compared to the fentanyl group, with a p-value of 0.001, which is similar to the present study [11]. Sonya K and Davies CV, in their study, found that buprenorphine had a prolonged duration of sensory block of 317 minutes compared to the fentanyl group, which was 214 minutes (p-value 0.000005) [12]. However, in their study, they did not find any significant difference in the mean regression time of motor block in either group (p-value 0.2239).

Authors	Sample size	Study place and year	Local anaesthetic drug	Adjuvant	Results
Patel N (Present study)*	80	Pune (2021-2022)	1.8 mL 0.5% Bupivacaine Heavy	Group B: 60 mcg Buprenorphine Group F: 25 mcg Fentanyl	Postoperative analgesia was significantly longer in Group B (304.63±40.58 min) as compared to Group F (228.63±32.68 min)
Ravindran R et al., [6]	90	Kerala (2017)	9 mg 0.5% Bupivacaine Heavy	Group A: 45 mcg Buprenorphine Group B: 60 mcg Buprenorphine Group C: 0.2 ml normal saline	Postoperative analgesia was significantly longer in Group A (6.11±5.18 hr) and Group B (12.3±6.5 hr) as compared to Group C(2.76±1.39 hr)
Sittaramane S et al., [9]	50	Tamil Nadu (2017)	7.5 mg 0.5% Bupivacaine Heavy	Group A: 60 mcg Buprenorphine Group B: 25 mcg Fentanyl	Duration of analgesia was significantly longer in Group A (200.32±9.1 min) as compared to Group B (491±153.97 min)
Pathak DB and Engti P [11]	50	Assam (2020)	15 mg 0.5% Bupivacaine Heavy	Group A: 75 mcg Buprenorphine Group B: 25 mcg Fentanyl	Duration of analgesia was significantly longer in Group A (295.82±10 min) as compared to Group B (196±10 min)
Sonya K and Davies CV [12]	60	Kerala (2017)	1.8 ml 0.5% Bupivacaine Heavy	Group B: 75 mcg Buprenorphine Group F: 25 mcg Fentanyl	Duration of analgesia was significantly longer in Group B (317±54 min) as compared to Group F (214±35 min)
Singh Y et al., [13]	60	Varanasi (2022)	2.5 ml 0.5% Bupivacaine Heavy	Group B: 75 mcg Buprenorphine Group F: 25 mcg Fentanyl	Duration of analgesia was significantly prolonged in Group B (516.50±47.25 min) as compared to Group F (371.20±60.03 min)
Jejani AK et al., [14]	60	Wardha (2019)	10 mg 0.5% Bupivacaine Heavy	Group A: 45 mcg Buprenorphine Group B: 1.5 ml normal saline	Duration of analgesia was significantly longer in Group A (795.33±261.49 min) as compared to Group B (294±76.13 min)
Grandhi MP and Reddy SPK [15]	63	Andhra Pradesh [2020]	1.6 ml 0.5% Bupivacaine Heavy	Group B: 60 mcg Buprenorphine +0.2 mL distilled water Group F: 20 mcg Fentanyl	Significantly prolonged effective analgesia time in Group B (547.60±80.276 min) as compare to Group F (410.00±67.942 min)

[Table/Fig-8]: Showed comparison of postoperative analgesia between the present study and similar published studies [6,9,11-13,14,15].

The mean time to request the first rescue analgesia for pain in Group B and Group F was 304.63 minutes and 228.63 minutes, respectively. The minimum-maximum time range for the first rescue analgesia in Group B was 195-360 minutes, and in Group F it was 160-300 minutes. The duration for the first rescue analgesia is significantly longer in Group B compared to Group F (p-value <0.05) [Table/Fig-4].

In a study by Singh Y et al., they found that the duration of analgesia was significantly prolonged in the buprenorphine group (516.50 minutes) compared to the fentanyl group (371.20 minutes) (p-value <0.001) [13]. This is in accordance with the findings of the present study [Table/Fig-8] [6,9,11-13,14,15]. The greater affinity for opioid receptors and low dissociation of buprenorphine may be the reasons for its prolonged action [16].

The distribution of mean pain scores (VAS) at 2 hr, 3 hr, and 4 hr among the cases studied shows that the analgesia produced by fentanyl wore off much quickly compared to patients receiving buprenorphine (p-value <0.05 for all). This indicates a shorter total duration of fentanyl, thus requiring earlier rescue analgesia. The distribution of mean pain scores (VAS) at 6 hr among the cases studied is significantly higher in Group B compared to Group F (p-value <0.05). Group B suggests a prolonged duration of analgesia until this point [Table/Fig-4].

Sonya K and Davies CV reported similar findings with a much longer analgesia time in patients receiving buprenorphine (317 minutes) compared to fentanyl (214 minutes) (p-value=0.000005) [12]. Sittaramane S and Dhakshunamoorty in their study, found that the mean duration of effective analgesia was 200.32 minutes in the fentanyl group compared to 491.28 minutes in the buprenorphine group, which was highly significant statistically (p<0.01), without producing any maternal or neonatal side-effects [9].

The mean time for complete motor block in Group B and Group F was 222.00 seconds and 259.25 seconds, respectively. Patients receiving buprenorphine showed a faster onset of action, possibly due to the high solubility and high affinity of buprenorphine for the opioid receptor (p-value <0.05). This indicates that the addition of buprenorphine enhances the completion time for motor blockade. Jejani AK et al., in a study, found a significantly faster onset of complete motor blockade in the buprenorphine group (p-value=0.0001) [14].

No significant difference was observed in the mean time for the onset of sensory block and maximum sensory block in Group B and Group F (p-value >0.05), suggesting that the onset of bupivacaine-induced sensory block was not affected by any of the opioid adjuvants. Grandhi MP and Reddy SPK, in their study, found an onset of sensory block of 2.86±0.50 minutes in Group B and 3.05±0.55 minutes in Group F [15]. Pathak DB and Engti P, in their study, found similar findings for the onset of sensory block with 7.304±0.61 minutes in Group A and 7.042±0.57 minutes in Group B, which is in accordance with the present study [11].

The mean time for the onset of motor block in Group B (134.25±61.51) and Group F (158.87±70.90) did not differ significantly between the two study groups (p-value >0.05). In accordance with this, a study done by Sittaramane S and Dhakshunamoorty found that the onset of motor block was not significantly different between the buprenorphine group (160±22.3 sec) and the fentanyl group (159±20.31 sec) [9]. However, this is not in accordance with a study done by Nelamangala K et al., who found that the onset of motor blockade with fentanyl was significantly faster compared to the buprenorphine group (p-value=0.040) [17].

Assessment of the level of consciousness is necessary for early diagnosis and detection of respiratory depression and other side-effects due to opioids. No significant difference was found in the distribution of intra/postoperative mean RAMSAY Sedation scale among the cases studied, suggesting that there was no significant amount of sedation produced by both drugs (p-value >0.05 for all).

None of the patients in either group showed the incidence of intraoperative respiratory depression or vomiting. Buprenorphine-induced respiratory depression can be reversed with the first loading followed by continuous infusion of inj. Naloxone. There were no significant haemodynamic changes in either of the groups, such as bradycardia, hypotension, pruritus, or foetal hypoxia, with the addition of either opioid.

Limitation(s)

The sample size of the present study is relatively small (n=80), so the results may not be generalised to a larger population. Further studies with a larger sample size may be required. In present study, the postoperative analgesia period was monitored until the demand for the first rescue analgesia. It would have been beneficial to continue monitoring the required rescue doses for a 24-hour period.

CONCLUSION(S)

Although buprenorphine (a μ-agonist/κ-antagonist) and fentanyl (a pure μ-agonist) are pharmacologically different opioids, both are safe and suitable for addition along with hyperbaric bupivacaine 0.5% in spinal anaesthesia for LSCS. The buprenorphine group shows much superior intra/postoperative analgesia in terms of quicker onset, minimal effect on sympathetic activity, prolongation of the duration of sensory block/motor block, duration of postoperative analgesia, and time to rescue analgesia compared to the fentanyl group.

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