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A randomized double blind clinical study comparing low dose hyperbaric bupivacaine and fentanyl mixture to a conventional dose of hyperbaric bupivacaine for caesarean section

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Abstract
Introduction: Obstetric patients need strict dose calculations of local anesthetics, any greater dose can cause hemodynamic instability and lesser dose can produce inadequate block. Hence, we hypothesized in our study that by using low dose of bupivacaine with fentanyl can maintain stable hemodynamics and provide better analgesia.
Aim: To compare the hemodynamics and duration of analgesia using a low dose (7.5 mg) bupivacaine fentanyl mixture to a conventional dose (10 mg) of hyperbaric bupivacaine for cesarean section.
Design: Double-blinded, randomized, controlled prospective study conducted at a tertiary care hospital.
Materials and Methods: Sixty singleton parturient, scheduled for elective caesarean section were randomly allocated into two groups. Study group (group-BF) received a combination of 25 µg fentanyl and 7.5 mg of hyperbaric bupivacaine, whereas the control group (group-B) received 10 mg of hyperbaric bupivacaine. Maternal hemodynamics, sensory and motor block, duration of analgesia and Apgar score of new born were compared between the groups.
Results: The time of onset of sensory analgesia and the time taken to achieve the highest sensory level was more in Group B than in Group BF which was statistically significant. The mean height of sensory analgesia was T4 (T3-T6) in both the groups. The mean time taken for two segment sensory regression and the mean time for sensory regression to L1 was prolonged in Group BF than in Group B which was statistically significant. The mean time of onset of Grade III motor block and the mean duration of motor block was more in Group B than in Group BF which was not statistically significant. Hemodynamic parameter HR, SBP, DBP changes per minute recorded in Group B and BF were almost similar & statistically not significant
Conclusion: The combination of low dose bupivacaine and fentanyl in comparison to bupivacaine alone has augmented the onset and prolonged the duration of sensory blockade. Onset and duration of motor block, intraoperative hemodynamic changes were comparable in both groups.

Keywords: hyperbaric bupivacaine, fentanyl, combination

1. Introduction

The greatest gift God has given to mankind is not in happiness, but in relief of pain.In pursuit of relief of pain manyattempts have been made since time immemorial. Spinal anesthesia was introduced into clinical practice by Karl August Bier in 1898 [1]. More than a century has passed and even today, it is one of the most popular techniques for both elective and emergency surgical procedures particularly Caesarean Sections, lower abdominal surgeries, orthopedic and urological surgeries just to name a few [2]. Spinal anesthesia, defined [3], as *'the regional anesthesia obtained by blocking nerves in the subarachnoid space'* is a popular & common technique used worldwide. The advantages of an awake patient, simple to perform, rapid onset of action, minimal drug cost, relatively less side effects & rapid patient turnover has made this the choice of procedure for many. Bupivacaine, an amide type of LA was introduced by Ekenstam in 1957 and first used clinically by Telivuo in 1963 [4]. It is the most commonly employed LA intrathecally for caesarean section. It is well known that the dose of the drug influences the duration of sensory as well as motor blockade and has a significant effect on the degree of hypotension [5]. However, intrathecal bupivacaine alone may be insufficient to provide complete analgesia despite high sensory block. 13% of the patients undergoing caesarean delivery had visceral pain even after the intrathecal administration of 15 mg of bupivacaine. Many mothers require supplemental analgesics to relieve pain associated with exteriorization of the uterus and traction on the abdominal viscera. Large doses are associated with higher block during spinal anesthesia [6, 7, 8]. Hence adjuvants are added to decrease the dose of LA required [9]. When only LAs were used, high doses of post operative Morphine and other opioids were required to provide adequate post operative analgesia [10]. Adjuvant like opioids (Morphine, Fentanyl, Sufentanyl) and non-opioids like α-2 adrenergic agonists (Clonidine, Dexmedetomidine), anti cholinesterases (Neostigmine), Midazolam, steroids and Ketamine were used [11]. These adjuvant improved the quality of intra operative

anesthesia and prolonged the duration of post operative analgesia. Therefore smaller doses of bupivacaine supplemented by intrathecal opioids have been recommended for spinal anesthesia in parturient undergoing caesarean section [12, 13, 14]. Neuraxial administration of opioids in conjunction with LAs improves the quality of intraoperative analgesia and also enhances the duration of postoperative analgesia [15]. Animal studies have demonstrated antinociceptive synergism between intrathecal opioids and LAs during visceral and somatic nociception [16, 17, 18]. Morphine, a hydrophilic agent may not be optimal as an intrathecal drug for intraoperative analgesia because of its slow onset of action. Morphine has prolonged duration of action and delayed respiratory depression is not infrequent following spinal administration. Fentanyl, a lipophilic opioid, has rapid onset of action after intrathecal administration. It does not tend to migrate to 4th ventricle in sufficient concentrations to cause delayed respiratory depression when administered intrathecall [19]. After intrathecal (IT) fentanyl administration, it diffuses into epidural space and subsequently into the plasma, suggesting that IT fentanyl not only act through spinal opioid receptors but also act systemically. Therefore fentanyl provides better intraoperative analgesia [20]. This study was designed to compare the hemodynamic changes and duration of analgesia using a low dose (7.5 mg) bupivacaine fentanyl mixture to conventional dose (10 mg) of hyperbaric bupivacaine for cesarean section.

Aim

To compare the hemodynamic changes and duration of analgesia using 7.5mg of 0.5% hyperbaric bupivacaine with 25mcg of fentanyl mixture to 10mg of 0.5% hyperbaric bupivacaine for caesarean section.

Objectives

To compare onset and duration of sensory blockade, to study hemodynamic parameters and intra-operative complications, to compare onset and duration of motor blockade, to compare total duration of analgesia and to study intra-operative complications.

Methodology

This prospective, randomized, double blinded clinical study was conducted on 60 parturient females of ASA I & II scheduled for elective caesarean section at Krishna Hospital and Medical Research Centre, Karad, from December 2015 to November 2017, for 24 months duration, after approval from institutional ethics committee. Written informed consent was obtained prior to enrolment of subjects in the study.

Sample size: The statistical power analysis suggested that a sample size of 25/group is required to achieve a power of >95% and alpha value as low as 0.001 to be able to detect a difference of total duration of analgesia of at least 50 min between the groups. But however we included 30 samples in each group for better validation of result. So based on data from previous study Venkata *et al.* [21] and the statistical formula, the total sample size was calculated to be 60 (30 patients in each group).Parturient females between the age of 18 and 40 years scheduled for elective caesarean section, belonging to American Society of Anesthesiologists (ASA) physical status I and II were considered for inclusion in the study. Parturient with pre-existing hypertension or pregnancy induced hypertension, cardiac/renal or other end-organ disease in active labor, twin pregnancy, placenta previa, neurological dysfunction, bleeding or coagulation disorder, deformed spinal column, infection at site of lumbar puncture, allergy to local anesthetic amides, refusal to technique, obesity (bmi>30), extreme height (<150 cm or >180 cm) were excluded from the study.

Methods

Each patient was visited before surgery. A detailed history, complete physical examination, systemic examination and pre-operative investigations including complete haemogram with platelet count, bleeding time, clotting time, blood sugar &urea, x-ray chest PA view, ECG were done for all patients. Accordingly patients were assigned into ASA groups. Informed consent was obtained from all the patients fulfilling the inclusion criteria after explaining the study in detail in his/ her own language in presence of a witness. 60 parturient females were randomly divided into 2 groups (Group BF and Group B) with 30 patients in each group. Group-BF was given Intrathecal 0.5% hyperbaric bupivacaine 7.5 mg (1.5 ml) with 25 mcg fentanyl 0.5ml (Total volume = 2 ml) and Group B was given Intrathecal 0.5% hyperbaric bupivacaine 10 mg (2 ml).Randomization was done with coded slips and accordingly, that study drug was given to the patient and drug code was recorded in patient´sproforma. During the study conducted in a double blind procedure, the technical part was handled by one set of anesthesiologists and the observational part was left to different set of anesthesiologists.

Preparation of the patient

The routine preparations were carried out as required for surgery and informed written consent was obtained. The anesthesia machine checklist and necessary drugs were kept ready. An intravenous line was secured with 18G IV cannula. Preloading was done with 500 ml of ringer's lactate over 15 minutes. Inj. metaclopromide 10 mg I.V. and Inj. ranitidine 150 mg I.V. was given 30 minutes prior to shifting patient to operation theatre. Monitors were connected. Baseline reading of pulse rate, blood pressure, arterial oxygen saturation (SPO_2), respiratory rate and fetal heart sounds were noted.

Performing the subarachnoid block

The patient was placed in left lateral position on an operation table. Under strict aseptic precautions lumbar subarachnoid block was performed using 25 gauge Quincke type spinal needle and after clear free flow of CSF the drug was injected slowly over 20 seconds, with the bevel of the spinal needle pointing cephalad. The total volume was 2 ml in both the groups. The patient was turned on the back immediately, placed in a supine position and 10 cm wedge placed under the right hip. After spinal anesthesia, oxygen (4L/min) by facemask was given. .Fluid therapy was maintained with lactated ringer's solution (10mL/kg/hr). Patients were monitored continuously using non invasive blood pressure, pulse oximeter and electrocardiogram. Sensory and motor assessment was performed immediately. Surgical incision was allowed when sensory level was at or above T6 dermatome

and motor blockade was adequate. Observations were recorded. All the patients were assessed for time of onset of sensory analgesia to T10, highest level of sensory analgesia, time taken to achieve highest level of sensory analgesia, time for two segment sensory regression, time for sensory regression to L1, total duration of analgesia, time of onset of grade 3 motor block, total duration of motor block, APGAR at 1 and 5 minutes interval, cardiovascular parameters, respiratory parameters, side effects like nausea, vomiting, respiratory depression, shivering, pruritus, etc. if any.Sensory level of the block was assessed by loss of cold sensation bilaterally at 2 min intervals and confirmed by a pinprick method. Motor block in the lower limb was graded according to modified Bromage scale.

Definitions used in the study were:

Table 1

Time of onset of sensory analgesia to T10	Time taken from the completion of the injection of the study drug till the patient does not feel the pin prick at T10 level
Highest level of sensory analgesia	Maximum sensory level attained
Time taken for highest level of sensory analgesia	The time from the completion of the injection of the study drug to the maximum sensory blockade attained
Time for two segment sensory regression	Time from maximum attainment of sensory block to regression of blockade by two segments
Time for sensory regression to L1	Time taken for sensory regression to L1 dermatome
Total duration of analgesia	Time from drug injection to first request for analgesics
Time of onset of grade III motor blockade	Time taken from the completion of injection of the study drug till patient develops Bromage-scale 3
Total duration of motor blockade	The time taken from the time of injection till the patient attains complete motor recovery, Bromage-scale 0

During intraoperative period

After the block patient was monitored for pulse rate and blood pressure every 2 min for first 10 min and every 5 min up to 30 min and every 15 min up to one hour and every 30 min thereafter till the sensory block regresses to L1 During the procedure all patients were infused appropriate quantity of intravenous fluid. Any untoward side effects were noted (bradycardia, hypotension, pruritus, shivering, nausea and vomiting).APGAR score at 1 and 5 min was noted. Bradycardia: A pulse rate of less than 60 beats per minute was considered as bradycardia and if any was treated with injection atropine 0.6 mg intravenously. Hypotension: A systolic blood pressure of less than 90 mmHg or decrease in 30% below the baseline systolic blood pressure was considered as hypotension. It was corrected with rapid infusion of IV fluids. Oxygenation with face mask, foot end elevation and inj. mephentermine 6 mg IV if required was given.

Data Analysis

Interpretation of the data was carried out, and analyzed using Microsoft excel and by the software Statistical Package for Social Sciences SPSS .Data is represented as mean ± standard deviation for continuous data. The two groups were compared using analysis of variance to compare the demographic data and hemodynamic parameters. The proportion of adverse effects was compared using Chi-square test. P value was assessed by paired t-test and $P < 0.05$ was considered as statistically significant.

Results

Demographic data like age, weight, height, duration of surgery were comparable in both the groups and statistically insignificant as shown.

Table 2

Variables*	Group B	Group BF	P value
Age (years)	24.71± 3.89	24.27± 3.69	NS
Weight (kg)	62.5± 2.24	61.9± 2.44	NS
Height (cm)	163.33± 7.87	162.43±9.67	NS
Duration of Surgery (Min)	62.90 ± 12.12	62.64±10.63	NS

Values are in mean ± SD. ASA: American Society of Anaesthesiologists, SD: Standard deviation, NS: Not significant, Group C: Control, Group S: Study. *Statistically significant $P < 0.05$

Sensory and motor blockade

The time of onset of sensory analgesia and the time taken to achieve the highest sensory level was more in Group B than in Group BF which was statistically significant.

The mean height of sensory analgesia was T4 (T3-T6) in both the groups. The mean time taken for two segment sensory regression and the mean time for sensory regression to L1 was prolonged in Group BF than in Group B which was statistically significant.

The mean time of onset of Grade III motor block and the mean duration of motor block was more in Group B than in Group BF which was not statistically significant.

Total duration of analgesia

The mean time of total duration of analgesia was prolonged in Group BF than in Group B which was statistically significant.

Hemodynamic parameter

The HR, SBP, DBP changes per minute recorded in Group B and BF were almost similar & statistically not significant

Apgar

There was no statistically significant difference observed between APGAR

Score of Group B and BF.

Table 2

Variables*	Group B	Group BF	P value
Time of onset of sensory analgesia(min)	2.40± 1.69	1.88± 0.64	S
Time to achieve highest sensory level(min)	5.19 ± 1.91	3.87±1.87	S
Time for two segment sensory regression(min)	97.97±32.27	130.02±17.22	S
Time for sensory regression to L1(min)	178.97±45.07	272.06± 70.17	S
Time for sensory regression to L1(min)	178.97±45.07	272.06± 70.17	S
Time of onset of Grade III motor block(min)	3.09± 1.08	2.78 ± 0.91	NS
Duration of motor block(min)	180.11±27.33	171.21± 21.25	NS
Total duration of analgesia(min)	164.58±27.01	258.97±38.68	S

Complications

Hypotension was noticed in 40% of patients in Group B and 30% in Group BF. Bradycardia was noticed in 10 % of patients in Group B and 10 % of Patientsin Group BF. Nausea and vomiting was seen in 17.67% of patient in Group BF and 13.33% of patients in Group BF, p< 0.05 which is statistically Significant. Shivering was seen in 20% of the patients in Group B and 6.7% of the patients in Group BF, p< 0.05 which is statistically significant. None of the patients suffered from pruritus in Group B but in Group BF 6.7% of patient had suffered from itching. None of the patients complained of respiratory depression, foetal bradycardia, postdural puncture headache or neurological complication in the Group B and Group BF.

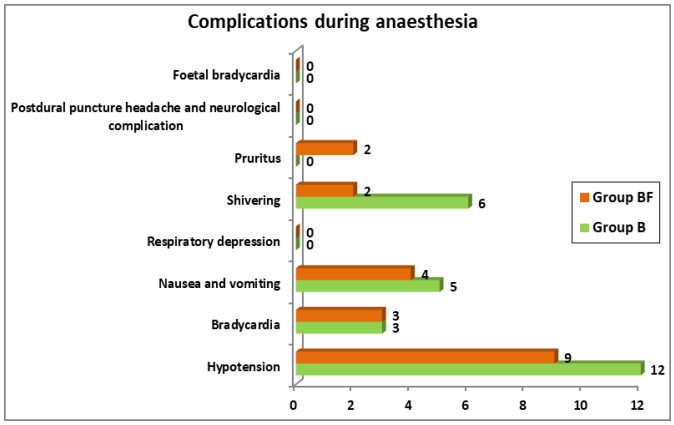

Fig 1

Discussion

The last two decades have seen an increase in the incidence of caesarean section. Spinal anesthesia is the preferred means for caesarean section. Bupivacaine is the LA used routinely for caesarean section because of its high potency and minimal neurological symptoms. The larger dose of LA is required to obliterate the visceral pain caused due to traction on peritoneum and intraperitoneal organs during caesarean delivery, but such large doses are associated with high levels of block and undesirable side effects. Opioids are well known to improve the analgesic potency of LA. If administered intrathecally a short acting lipophilic opioid is known to augment the quality of subarachnoid block. Hence the present study was conducted to compare the hemodynamics and duration of analgesia using 7.5mg of 0.5% hyperbaric bupivacaine and 25mcg of fentanyl mixture to 10mg of 0.5% hyperbaric bupivacaine for caesarean section. The study was done at Krishna Institute of medical science involving 60 ASA Grade I and II patients who underwent caesarean section under subarachnoid block.

Sensory Characteristics

The mean time of onset of analgesia at T10 in Group B was more than in Group BF and the difference was statistically significant (p<0.05). This showed addition of fentanyl to bupivacaine hastens the onset of sensory block. This is in accordance with the result of Venkata *et al.* [21]. In the present study, the highest sensory level range was T4 (T3-T6) in both Group B and Group BF. The mean time taken to achieve highest sensory level in Group B was more than in Group BF and the difference was statistically significant (p<0.05). This is in accordance with the result of Hunt *et al.* [14]. In the present study, mean time for two segment regression was prolonged in Group BF than in Group B and the difference was statistically significant (p < 0.05). So, time for two segment regression was prolonged with the addition of fentanyl to bupivacaine. This is in accordance with the result of Singh *et al.* [22] and Venkata *et al.* [21]. In the present study, the mean time for sensory regression to L1 was prolonged in Group BF than in Group B and the difference was statistically significant (p < 0.05). So addition of fentanyl prolonged time for sensory regression to L1. This is in accordance with the result of Biswas *et al.*, [23] and Singh *et al.* [22]. In the present study, the mean time for onset of grade III motor block was more in Group B than in Group BF and the difference was not statistically significant (p>0.05). So the addition of fentanyl to bupivacaine did not affect the onset of motor block. This is in accordance with the result of Hunt *et al.* [14], Singh *et al.* [22] and B is was *et al.* [23]. In the present study, the mean duration of motor block was less in Group B than in Group BF and the difference was not statistically significant (p>0.05). So the addition of fentanyl to bupivacaine did not affect the duration motor block. This is in accordance with the result of Biswas *et al.* [23] and Singh *et al.* [22]. In the present study, the mean duration of analgesia was prolonged in Group BF than in Group B and the difference was statistically significant (p < 0.05) which indicates the total duration of analgesia was prolonged with the addition of fentanyl in our present study. This is in accordance with the result of Biswas *et al.* [23] and Venkata *et al.* [21].

Hemodynamic changes

The mean value of SBP, DBP changes in mmHg and the mean values of pulse rate changes per minute recorded in Group B and Group BF were almost similar. This was statistically not significant. This is in accordance with the result of Biswas *et al.* [23], Singh *et al.* [22].

Complications

Nausea vomiting was seen in 16.67 % in Group B and 13.3%

in Group BF patients which was statistically significant ($p < 0.05$) .So addition of fentanyl to local anaesthetics reduced the perioperative nausea-vomiting. Shivering was observed in 20% of the patients in Group B and 6.7% Group BF, which was statistically significant ($p < 0.05$).Pruritus was observed in 6.7% of patients in Group BF and not observed in any patients in Group B, i.e. bupivacaine alone. Our results concurs with the results Siddik Sayyid *et al.* [24]. In the present study we did not notice any incidence of respiratory depression upto 24 hours postoperatively. Similar results were noticed in the studies conducted by Biswas *et al.* [23], Hunt *et al.* [14], Singh *et al.* [22] & Belzarena *et al.* [25]. None of the patients in this study experienced any neurological complication or PDPH during postoperative follow-up. None of the patients required supplementation with general anesthesia in our present study. There were no differences in neonatal APGAR scores among the groups, which were similar with observations of Biswas *et al.* [23], Hunt *et al.* [14], and Shende *et al.* [12] study.

Conclusions

From the present study it can be concluded that, the combination of low dose 0.5% hyperbaric bupivacain 7.5 mg (1.5 ml) with 25 mcg of fentanyl as adjuvant in spinal anesthesia for elective caesarean section had augmented the onset and prolonged the duration of sensory blockade compared to conventional dose of 0.5% hyperbaric bupivacain 10 mg (2 ml) .Onset and duration of motor block, intraoperative hemodynamic changes were comparable in both groups. Iontraoperative nausea, vomiting, shivering were less in those patients where low dose 0.5% hyperbaric bupivacain 7.5 mg (1.5 ml) with 25 mcg of fentanyl was used compared to those patients in which conventional dose of 0.5% hyperbaric bupivacain 10 mg (2 ml) was used .Total duration of analgesia was prolonged in those patients where low dose hyperbaric bupivacain 7.5 mg (1.5 ml) with 25 mcg of fentanyl was used compared to those patients in which conventional dose of 0.5% hyperbaric bupivacain 10 mg (2 ml) was used. Hence low dose hyperbaric bupivacain 7.5 mg (1.5 ml) with 25 mcg of fentanyl can be safely used for all patients undergoing elective caesarean section with rapid onset and prolonged duration of sensory blockade, minimal heamodyanmic changes, less intraoperative complication and prolonged total duration of analgesia .

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