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Original Research Article

Evaluation of intrathecal bupivacaine alone, bupivacaine with butorphanol and bupivacaine with dexmedetomidine for lower segment caesarean section: a randomized control trial

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ABSTRACT

Background: Following caesarean operation, a painless early ambulation is necessary to mother for caring of the neonate. Aim of the study is to compare more effective analgesic by intrathecal bupivacaine or combination with butorphanol or dexmedetomidine.

Methods: Ninety parturients undergoing elective caesarean section were randomly divided into three equal groups (n=30). Group B: received bupivacaine (0.5%) 2 ml + 0.5 ml of normal saline (NS); group BB, bupivacaine (0.5%) 2 ml + 25 mcg butorphanol in 0.5 ml NS and group BD, bupivacaine (0.5%) 2ml + 2.5 mcg of dexmedetomidine in 0.5 ml NS . Visual numerical rating scale (VNRS), heart rate, blood pressure, sensory and motor block levels, fetal outcome by Apgar score and umbilical cord blood pH, any side effects were noted.

Results: The onset time of modified Bromage 3 motor block was statistically significant among the groups (P=0.023) but not significant between Groups BB and BD (P=0.479). The regression time to reach modified Bromage 0 in group BD was significantly longer (P=<0.0001) than either of the groups B or BB but not significant between the later two groups (P=0.479). Time for 2-segment regression, sensory regression time to S1 dermatome and time for first rescue analgesia were significantly longer (P<0.001) in group BD but not significant between the groups B and BB. Sedation was significantly more in group BD (17/30 pts; P<0.001).

Conclusions: Addition of dexmedetomidine to spinal bupivacaine block in caesarean section increase the duration of analgesia and motor block with minimal side effect and no adverse effects on the babies.

Keywords: Bupivacaine, Butorphanol, Dexmedetomidine, Caesarean Section, Spinal anaesthesia

INTRODUCTION

The need for early ambulation for caring of the neonate by mother makes postoperative pain management after caesarean delivery unique. To achieve this, various drug combinations and techniques have been tried to find out the more effective and safer analgesia. Most breast feeding women may choose to limit their systemic analgesic doses. Neuroaxial analgesic technique are gold standards for pain relief during labour and delivery.[1] The intrathecal opioids have been used to increase the duration of postoperative analgesia without affecting the sympathetic and motor functions.[2]

Opioids with μ-receptor agonists like fentanyl, buprenorphine, etc. have been tried extensively for this purpose. However, side effects due to μ-receptor stimulation like respiratory depression, pruritus, urinary retention and abuse liability remain a concern.

To alleviate this problem alpha agonist like clonidine have been used alone or in combination with opioids for lower abdominal surgery and labour analgesia.[3-6] Despite increasing the duration of postoperative analgesia, alpha2 agonist also causes side effects like sedation, dryness of mouth and hypotension specially in higher dose. Dexmedetomidine is another highly selective alpha2 agonist which has been used in surgical patients

intrathecally to prolong the duration of postoperative analgesia.[7-9] However there has been some reluctance on its use in obstetric patients for fear of uteroplacental transfer and untoward effects on the baby and its reckless administration could have posed difficult challenges to both mother and neonate.[10] However, dexmnedetomidine is a highly lipid soluble drug with retention of the placenta (maternal to fetal index of 0.77) and it virtually do not cross the placenta.[11] And, there are numerous case reports of its successful use in obstetrics without adverse effects on fetal outcome. A recent randomized controlled trial has found intrathecal dexmedetomidine to significantly prolong the duration of labour analgesia. However, the associated prolongation of motor block may not be desirable in some obstetric patients.

Hence, the search of an opioid which can prolong the duration of analgesia but without μ-receptor related side effects like pruritus and nausea become imperative. Butorphanol to antagonize pruritus and nausea produced by morphine (μ-agonist) while prolonging the duration of analgesia.[15] Two recent randomized controlled trials have also found intrathecal butorphenol to significantly prolong the duration of postoperative analgesia.[16,17] With this background, we have decided to compare the effects of intrathecal bupivacaine, alone or combination with butorphenol or dexmedetomidine during caesarean section delivery.

METHODS

Following clearance from the institutional ethics committee, this study was conducted in a tertiary teaching institute in Imphal, Manipur between November 2014 and August 2016. Ninety purturients with singleton pregnancy posted for elective caesarean section were selected in this prospective, randomized, double blinded study. Sample size was calculated based on a previous study to detect a difference of 30% (or approximately 60 minute) in the duration of analgesic for alpha value of 5% and power of 80%.[3]

Inclusion criteria

1. ASA (American society of Anaesthesiologist) grade I and II
2. Age: 18 to 40 years
3. Height: 150 to 165 cm
4. Weight: 50 to 70 kg

Exclusion criteria

1. Un co-operative patients
2. Patients refuse to give consent for anaesthesia
3. Patients with contraindication to spinal anaesthesia
4. Known allergy to study drugs

Using a computer generated random number, patients were allocated into three groups consisting of thirty patients in each group (n=30). Group B received intrathecal bupivacaine (0.5%) 2ml plus 0.5 ml of normal saline (NS). Group BB received the same amount of bupivacaine plus 25 microgram (mcg) butorphanol diluted in NS to make 0.5 ml. Group BD received similar amount of bupivacaine plus 2.5 mcg of dexmedetomidine diluted in NS to make 0.5 ml.

Preoperative evaluation was done a day before surgery. During preoperative visit patients were convinced about verbal numerical rating scale (VNRS) (0=no pain, 10=worst pain imaginable).[18] Patients were premedicated with tablet Ranitidine 150 mg the previous night before surgery as well as injection Ranitidine 50 mg and injection Metoclopramide 10 mg intravenously 1-2 hours before caesarean section. Upon arrival of patient into the operating room, electrocardiogram (ECG), pulse oximetry (SPO2) and non-invasive blood pressure (NIBP) were monitored. Following infusion of 10-15 ml/kg of Lacted Ringer solution over approximately 15 minutes, patients were placed in the left lateral position. Blinding was done by an assistant anaesthesiologist preparing the drug before intrathecal injection by the primary investigator. Under aseptic and antiseptic precaution the subarachnoid block was given into the L_{3-4} intrathecal space using a 25G Quincke spinal needle (B.Braun) at a rate of 0.2 ml/sec. After intrathecal injection, patients were positioned in supine position with a wedge below the right buttock to elevate it 20-30 degree to avoid aorto-caval compression. Oxygen 2 liters per minute was given through a face mask to maintain spo2 of >92% at room air. Vital signs were recorded every 2 minutes for first 20 minutes then every 5 minutes intraoperatively and every 15 minutes in the post anaesthesia care unit (PACU). Hypotension (systolic blood pressure <90 mmHg or fall of > 20% from base line) was corrected by intra venous fluid bolus of 200 ml and/or incremental injection of mephentermine 3 mgiv bolus. Injection atropine 0.3-0.5 mg IV was kept ready for persistent bradycardia (heart rate <50 beats/minute).

The sensory block level was assessed by pin prick method along the midclavicular line bilaterally. The motor block was assessed according to the modified Bromage scale by the time when sensory block level reach T_{10} (Bromage 0: free movement of legs and feet; Bromage 1: just able to flex knee with free movement of feet; Bromage 2: unable to flex knees, but with free movement of feet; Bromage 3: unable to move legs or feet) the onset of sensory block will be taken as the time when the patient first complain of tingling and numbness upon questioning from intrathecal injection.[19] The time to reach T_{10} dermatome sensory block, peak sensory block level and Bromage 3 motor block were recorded before surgery. The regression time for sensory and motor block were recorded in PACU. All durations were calculated considering the time for spinal injection as time zero. Assessment of pain during intraoperative and post-operative period (PACU) was done using VNRS. Injection diclofenac 75 mg IM was given as rescue

analgesic when VNRS >5. Sedation was assessed using outcome and assessment information set (OASIS), a sedation scale.[20] Other side effects like nausea, vomiting, pruritus and shivering were recorded. Patients were discharged from PACU after sensory regression to S_1 and motor regression to Bromage I.

Fetal outcome was assessed by Apgar score (1 minute and 5 minute) and umbilical cord blood pH. Outcome was labelled good if Apgar score ≥7 (1min) or ≥9 (5 min), and umbilical cord pH within reference value (≥7.2-7.4).

Statistical analysis

Statistical analysis was done by using statistical package for social sciences (SPSS version 21. Independent sample t test and ANOVA (F-test) were used for analysis of continuous variables of two and more groups separately. Categorical data were analysed using Ch-square tests, P-value of <0.05 was considered significant.

RESULTS

All the groups were comparable and found no statistical difference in patient's demographic profile as well as the duration of surgery and intra operative use of vasopressors (Table 1). Table 2 shows onset of sensory block (first complain of tingling and numbness in the lower limbs upon questioning following intrathecal injection) which was not different among the three groups (27.13±13.03 sec, 31.67±13.08 sec and 34.73±96 sec in group B, BB and BD respectively; P=0.537). Similarly the onset time of sensory block to reach T_{10} dermatome was 122. 57 ±45.26 sec for group B, 144.43±87.85 sec for group BB and 130.27±41.93 sec for group BD (P=0.527). The time to reach peak T_{4-6} sensory block level was 742.80 ±89.75 sec in group B, 297.50±115.15 sec in group BB and 222.67±65.96 sec in group BD (P=0.196) respectively. There was no significant difference in the median block height (group B: T_5, group BB: T_4 and group BD: T_6; P=0.602) The onset time of modified Bromage 3 motor block was found significant (P=0.023) among the three groups. This stems from significant difference between groups B and BD (165.83±75.49 sec versus 188.67±78.17 sec; P=0.017) but not between groups BB and BD (198.37±92.46 sec versus group B (188.67±78.17 sec; P=0.239). The regression time to reach modified Bromage 0 in group BD (208.33±62.70 sec) is significantly longer (P<0.0001) than either of group BB (194.60±87.71 sec) or group B (169.73±56.44 sec). There was no significant difference between the later two groups (P=0.479). Time for two – segment regression was significantly (P<0.001) longer in group BD compare to group BB and group B (173.17±57.26 min, 148.37±56.51 min and 140±52.30 min respectively). But the difference between group B and group BB was not significant (P=0.944). Similarly sensory regression time to S_1 dermatome was also significantly (P<0.001) longer in group BD when compare to either group BD or group B (198.43±72.34 min versus 179.43±73.53 min and 162.03±56.49 min respectively). Again the difference between group B and group BB is not significant (P=0.566). Time of first rescue analgesic is significantly (P<0.001) longer in group BD (221.93±62.61 min) compared to group BB (135.20±18.26 min) and group B (138.43±31.24 min). No significant (P=0.952) difference could be found between the later two groups.

Table 1: Demographic profile.

Parameters	Mean ± SD			F	P value
	Gr B (n=30)	Gr BB (n=30)	Gr BD (n=30)		
Age (years)	29.87±5.673	31.68±5.436	30.07±6.648	1.260	0.289
Weight (Kg)	59.20±5.281	61.33±5.241	59.87±4.023	0.785	0.439
Height (cm)	154.90±4.873	156.10±4.802	156.80±4.574	1.371	0.259
Gestational age (wks)	268.10±5.622	267.70±5.370	267.30±5.247	0.164	0.849
Duration of Surgery (min)	40.37±4.206	38.97±4.781	38.10±5.101	1.478	0.157
Vassopressure used *	1.80±2.683	2.10±2.249	1.60±2.328	0.690	0.561
ASA grade (I:II)	27:3	29:1	30:0		0.776

*Mephentine injection in mg.

The mean values of the HR, SBP, DBP and MAP were comparable among the three groups (Fig.1 to 4). Rescue analgesia was given in all the three groups (Table 3) even though the number is significantly less in group BD. The Apgar score and the umbilical venous blood pH did not show significant differences between the groups in this study as shown in Table 4. Table 5 shows no significant difference in side effects like hypotension, bradycardia, vomiting, dry mouth and pruritus. One patient each (3.3%) complained of nausea and shivering in group BD and B. Sedation was significantly (P<0.001) more in groups BB (4 patients; 13.3%) and BD (17 patients; 56.7%). No patients in group B had sedation. None of the patients complained of post dural puncture headache.

DISCUSSION

This study was conducted to compare the effects of intrathecal bupivacaine, alone or in combination with butorphanol or dexmedetomidine during caesarean section delivery. The rationale for choosing lower doses of dexmedetomidine or butorphanol was based on earlier studies.[14,16,17,21-24] Intrathecal dexmedetomodine in combination with bupivacaine have been studied in human beings without any postoperative neurological deficit.[8,23,25,27]

Table 2: Block characteristics.

Parameters	Mean ± SD			t	P-value
	Gr I (B)	Gr II (BB)	Gr III (BD)		
T onset $_0$ (sec)	27.13±13.030	31.67±13.082	34.73±13.958		0.537
T $_{10\ (sec)}$	122.57±45.258	144.43±87.845	130.27±41.928		0.527
T peak (T_{4-6}) in sec	242.80±89.753	297.50± 115.148	222.67+65.959		0.196
Median block height (min)	T_5	T_4	T_6		0.602
†T two segment sensory regression (min)	140+52.300	148.37+56.503	173.17+57.257		0.001
†T sensory regression to S_1 (sec)	162.03+56.485	179.43+73.532	198.43+72.336		0.001
Time of 1st rescue analgesic (if VNRS>5)	138.43+31.237	135.20+18.258	221.93+62.614		0.001
T $_{MB\ 1\ (sec)}$	120.03+39.018	135.7+68.476	121.10+32.127		0.203
T $_{MB\ 3(sec)}$	165.83+75.490	198.3+92.460	188.67+78.169		0.023
* T $_{MB\ 3\text{-}0\ (sec)}$	169.73+56.443	194.60+87.710	208.3+62.704		0.001

† Not significant difference between I & II; *not significant between I and II.

Table 3: Comparison of analgesic drug requirement post-operatively among the three groups.

Parameters	Status	Gr I (B)	Gr II (BB)	Gr III (BD)	X^2 Value	P Value
Analgesic dose <6 hrs	Not given	2 (6.7%)	1 (3.3%)	7 (23.3%)	6.975	0.031
	Given	28 (93.3%)	29 (96.7)	23 (76.7%)		
Analgesic dose 612 hrs	Not given	3 (10%)	6 (20%)	14 (46.7%)	11.330	0.003
	Given	27 (90%)	24 (80%)	16 (53.3%)		
Analgesic dose >12 hrs	Not given	27 (90%)	25 (83.3%)	18 (60%)	8.614	0.013
	given	3 (10%)	5 (16.7%)	12 (40%)		

Table 4: Comparison of Apgar score (in 1 min and 5 min) and umbilical cord pH among the three groups.

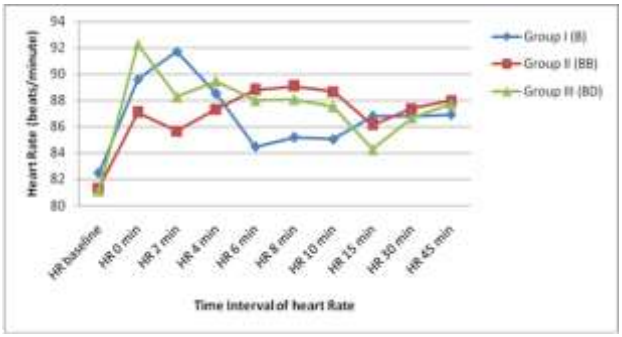
Parameters	Mean ± SD			P value
	Gr I (B)	Gr II (BB)	Gr III (BD)	
Apgar score 1 min	9±0	9±0	8.967±0.1826	0.372
Apgar score 5 min	9±0	9±0	9±0	-
Umbilical venous blood pH	7.33443±0.008135	7.33367±0.004901	7.33200±0.004068	0.276

The present study has shown that addition of dexmedetomidine 2.5 mcg to spinal bupivacaine significantly prolonged both sensory and motor block compared to the other two groups. However time for first rescue analgesia in our study is much less (221.93±62.61 min versus 478.4±20.9 min) than some earlier study probably due to the use of higher dose of dexmedetomidine in the later study.[7] Some earlier studies have also shown dose dependent prolongation of the duration of analgesia.[25,26] We opted for the lower dose to avoid hypotension and bradycardia as has already shown by Kenai et al.[23]

It is well known that intrathecal administration of local anaesthetics reduce blood pressure by decreasing sympathetic outflow. However, alpha-2 agonist, when co-administered with bupivacaine intrathecally did not show a further decrease in blood pressure presumably because the blockade produced by bupivacaine is nearly maximum.[28] In this study the median block height was not affected by the addition of dexmeditomidine. Similarly opinion is held by some similar study.[29]

Table 5: Comparison of side effects among the three groups.

Parameters	Status	Gr I (B)	Gr II (BB)	Gr III (BD)	X^2 value	P value
Hypotension	Absent	19 (63.3%)	14(46.7%)	18(60%)	1.900	0.387
	Present	11(36.7%)	16(53.3%)	12(40%)		
Bradycardia	Absent	30	30	30	-	-
	Present	0	0	0		
Nausea	Absent	30	30	29(96.7%)	2.022	0.364
	Present	0	0	1(3.3%)		
Vomiting	Absent	30	30	30	-	-
	Present	0	0	0		
Shivering	Absent	29(96.7%)	30	30	2.022	0.364
	Present	1(3.3%)	0	0		
Sedation	Absent	30	26(86.7%)	13(43.3%)		P<0.001
	Present	0	4(13.3%)	17(56.7%)		
Dry mouth	Absent	30	30	30	-	-
	Present	0	0	0		
Pruritus	Absent	30	30	30	-	-
	Present	0	0	0		

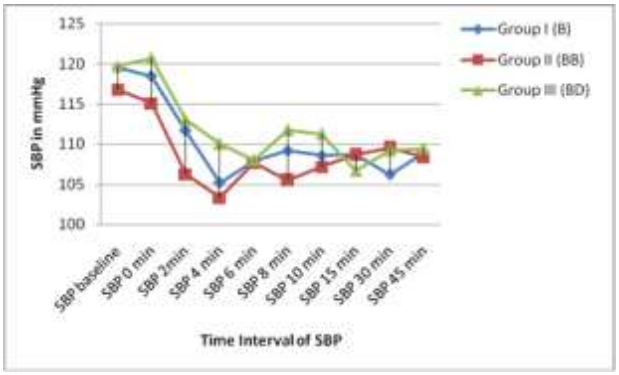


No significant difference among the three groups.

Figure 1: Comparison of intra-operative HR (beats/min) among the groups of patients studied.

The mechanism by which alpha-2 adrenoreceptor agonist prolong sensory and motor block of local anaesthetics may be depression of the presynaptic C-fibres and hyper polarization of postsynaptic dorsal horn neurons as well as binding to motor neurons in the dorsal horn.[30,31]

We did not come across any adverse neonatal outcome in terms of Apgar score at 1 and 5 minutes as well as umbilical vein blood PH. This is in agreement with earlier studies.[12,13] However the incidence of sedation in the mother is significantly more in the dexmedetomidine group. No special treatment was required for it.

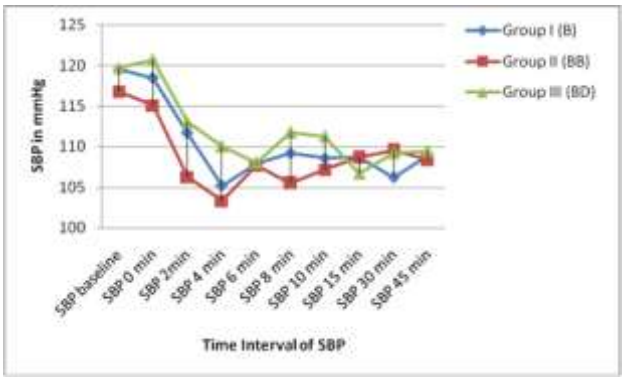


No significant difference among the three groups.

Figure 2: Comparison of intra-operative SBP among the three study groups.

Following the first intrathecal use of opioid by Wang JK et al., neuroaxial administration of opioids in conjunction with local anaesthetics have been shown to improve the quality of intra-operative analgesia with prolongation of the duration of postoperative analgesia.[32,33] Intrathecal opioids act by opening K^+ channels and reducing Ca^{++} influx, resulting in inhibition of transmitter release. They act synergistically with local anaesthetics to enhance somatic analgesia without an effect on the degree of local anaesthetic-induced sympathetic or motor blockade.[34,35] Addition of 25 mcg of butorphanol to intrathecal

bupivacaine have been shown to prolong the duration of post-operative analgesia.[16,17]



The marginal significant difference at 8th minute is due to difference between groups II and III (t =…….; P = 0.025).

Figure 3: Comparison of intra-operative SBP among the three study groups.

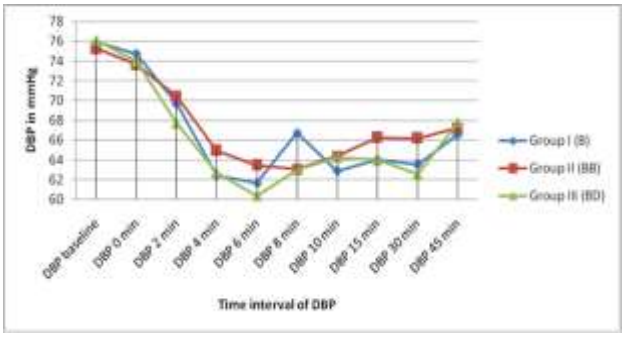


Figure 4: Comparison of intra-operative MAP among the three study groups.

In the present study we could not demonstrate any significant difference in the onset, peak sensory block level, time to two segment sensory regression or sensory regression to S_1 dermatome, time to first rescue analgesic or time to modified.

Bromage scale regression to 0 (Table 2). The reason for this apparent discrepancy with earlier studies is unclear because use the same dose of butorphanol (25 mcg) as in earlier studies.[16,17] We are also not sure whether the duration of analgesia is dose dependent to intrathecal opioids as one study [33] could not demonstrate it as the dose of intrathecal fentanyl was increased from 10 mcg to 40 mcg. This is in contrast to intrathecal dexmedetomidine which has dose dependent prolongation of postoperative analgesia. However failure of intrathecal opioids to prolong the duration of motor block is consistent with earlier studies.[16,24] Similarly μ-agonist related side effects like nausea, vomiting, pruritus, respiratory depression were not encountered with butorphanol (μ-antagonist and K antagonist) which is in agreement with the above mentioned studies. Four out of 30 patients (13.3%) in the butorphanol group had sedation. This finding is comparable to that of Vinila et al. who quoted an incidence of 20%. None of the patients required special treatment for it.[24] This incidence of sedation is significantly (P<0.001) less than that of dexmedetomidine group (17 out of 30; 56.7%).

We cannot explain the absence of prolongation of postoperative analgesia with intrathecal butorphanol added to bupivacaine compared to bupivacaine alone.

Though intrathecal dexmedetomidine has been shown to increase the duration of postoperative analgesia, the associated increase in the duration of motor block is not an advantage for mothers caring for her new-born babies.

CONCLUSION

Intrathecal dexmedetomidine supplementation of spinal block increase the duration of analgesia and motor block with mild sedation. The associated increase in motor block may be an advantage for major lower abdominal surgery (like abdominal hysterectomy) but not for caesarean section. We could not demonstrate intrathecal butorphanol added to bupivacaine superior to bupivacaine alone.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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