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The effects of addition of dexmedetomidine to intrathecal hyperbaric 0.5% bupivacaine in elective lower segment caesarean section:A prospective, randomized, double blinded, placebo-controlled study

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Abstract
Background: Spinal anaesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. Dexmedetomidine, a new highly selective α2-agonist, is under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects.
Methods: Prospective double blinded, placebo-controlled study was undertaken in 60 patients allocated randomly by envelop method, divided into 2 groups (30 in each) between 18-50 years of age of either gender belonging to ASA class I and II scheduled for elective lower segment caesarean section. Group A received 2 mL of 0.5% hyperbaric bupivacaine and 0.2ml dexmedetomidine and Group B received 2ml of 0.5% hyperbaric bupivacaine with 0.2ml normal saline. The comparison was studied using the Chi-square test or Fisher's exact test as appropriate, with the P value reported at the 95% confidence interval. $P<0.05$ was considered statistically significant.
Results: The addition of dexmedetomidine resulted in a dose dependent prolongation of sensory regression to S1 segment, prolonged motor block, the time to first analgesic rescue was significantly prolonged in Group B as compared to Group A and showed Lower pain scores as compared to placebo group.
Conclusion: Based on study results we recommend addition of dexmedetomidine 5 µg to intrathecal hyperbaric 0.5% Bupivacaine 9 mg in elective lower segment caesarean section.
Keywords: Anaesthesia, dexmedetomidine, intrathecal anaesthesia, local anaesthetic

Introduction
Spinal anaesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. However, postoperative pain control is a major

problem because spinal anaesthesia using only local anaesthetics is associated with relatively short duration of action, and thus early analgesic intervention is needed in the postoperative period. A number of adjuvants, such as clonidine and midazolam, and others have been studied to prolong the effect of spinal anaesthesia [1]. A common problem during lower abdominal surgeries under spinal anaesthesia is visceral pain, nausea, and vomiting. Dexmedetomidine, a new highly selective α2-agonist, is under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects [2]. Dexmedetomidine has been approved by Food and Drug Administration (FDA) as a short-term sedative for mechanically ventilated Intensive care unit (ICU) patients. Intravenous dexmedetomidine has been successfully used as an adjunct for labor analgesia and caesarean delivery, with favourable maternal and foetal outcome[3].Based on earlier human studies, it is hypothesized that intrathecal 5µg dexmedetomidine would produce more postoperative analgesic effect with hyperbaric bupivacaine in spinal anaesthesia with minimal side effects [4].

Materials and methods

The study was carried out at Bidar Institute of Medical Sciences, Bidar Karnataka from August 2020 to October 2021.The study was conducted after approval of ethical committee of the institution. Written informed consent was obtained from all patients. Inclusion criteria were American Society of Anaesthesiologists (ASA) physical status I or II, either gender, age 18–50 years, presenting for elective lower segment caesarean section. Exclusion criteria were patient allergic to drug, heart block/dysrhythmia, or on therapy with adrenergic receptor antagonist, calcium channel blocker, and/or Angiotensin-converting-enzyme (ACE) inhibitor.
The patients were preloaded with Lactated Ringer's solution 15 mL/kg. They were monitored with automated non-invasive blood pressure, pulse oximetry, and electrocardiogram. 25G Pencil point spinal needles were introduced through L3-L4 interspaces in sitting position using aseptic precautions. patients were allocated randomly by envelope method, using random number table into two groups (A and B) of 30 each: Group A received 2 ml volume of 0.5% hyperbaric bupivacaine and 0.2ml dexmedetomidine and Group B received 2ml volume of 0.5% hyperbaric bupivacaine with 0.2ml normal saline. Intrathecal injection was given over approximately 10-15s. Immediately after completion of the injection patients were made to lie supine. Oxygen (6 L/min) was administered via a mask if the pulse oximeter reading decreased below 90%. Hypotension, defined as a decrease of systolic blood pressure by more than 30% from baseline or a fall below 90 mmHg, was treated with incremental IV doses of ephedrine 5mg or mephentermine6mg and IV fluid as required. Bradycardia, defined as heart rate < 50 bpm, was treated with IV atropine 0.3-0.6 mg. The incidence of adverse effects, such as nausea, vomiting, shivering, pruritus, respiratory depression, sedation, and hypotension were recorded. Sensory testing was assessed by loss of pinprick sensation to 23G hypodermic needle and dermatomes levels were tested every 2 min until the highest level had stabilized by consecutive tests. On achieving T6 sensory blockade level, surgery was allowed. Testing was then conducted every 10 min until the point of two segment regression of the block was observed. Further testing was performed at 20-min intervals until the recovery of S2 dermatome. The surgeon, patient, and the observing anaesthesiologist were blinded to the patient group. Data regarding highest dermatome level of sensory blockade, the time to reach this level from the time of injection, time to S1 level sensory regression, time to urination, and incidence of side effects were recorded. Sedation was assessed by a modified Ramsay sedation scale (Table 1)[5]. Data regarding the Quality of motor blockade was assessed by Bromage scale (Table 2)[6].
Postoperatively, the pain score was recorded by using visual analogue pain scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain), initially every 1 h for 2 h, then every 2 h for the next 8 h and then after every 4 h till 24 h. Diclofenac 75mg iv was given

intramuscularly as rescue analgesia when visual analogue pain was >4. A follow-up was carried out 1 week postoperatively by the blinded anaesthesiologist, who asked about postoperative headache as well as postoperative pain and dysesthesia in the buttock, thighs, or lower limbs.

Statistical analysis was done using the Statistical Package for Social Science (SPSS15.0 Evaluation version). Continuous covariates were compared using analysis of variance (ANOVA). The comparison was studied using the Chi-square test or Fisher's exact test as appropriate, with the P value reported at the 95% confidence interval. $P<0.05$ was considered statistically significant.

Table 1: Modified Ramsay sedation scale

Score	Clinical state/Response to stimulus
1.	Awake and alert, minimal or no cognitive impairment.
2.	Awake but tranquil, purposeful responses to verbal commands at a conversational level.
3.	Appears asleep, purposeful response to verbal commands at a conversational level.
4.	Appears asleep, purposeful responses to commands but at a louder than conversational level, requiring light glabellar tap or both.
5.	Asleep, sluggish purposeful responses only to loud verbal commands, strong glabellar tap or both.
6.	Asleep, sluggish purposeful responses only to painful stimuli.
7.	Asleep, reflex withdrawal to painful stimuli only.
8.	Unresponsive to external stimuli, including pain.

Table 2: Bromage scale for assessing quality of motor blockade

Grade	Definition
0	Patient is able to move the hip, knee and ankle.
1	Patient is unable to move the hip but is able to move knee and ankle.
2	Patient is unable to move the hip and knee but is able to move the ankle.
3	Patient is unable to move hip, knee and ankle.

Results

There was no significant difference in the demographic data of the patients in between the 2 groups ($p>0.05$) (Table 3).Regarding the incidence of side effects, no statistically significant differences was observed in both the groups (Fig. 1).Tukey's multiple posthoc procedure showed that time taken to reach T10 dermatome and time for motor block to reach Bromage 3 was significant ($p<0.01$) in Group A vs Group B. (Table 4)

Time taken for sensory regression to S1: The addition of dexmedetomidine resulted in a dose dependent prolongation of sensory regression to S1 segment. The prolongation in time to regress in Group A vs group B was highly significant statistically by Tukey's test ($p<0.01$). Motor block regression to Bromage 0:Group B had a significantly prolonged motor block than group A. Statistical analysis by analysis of variance (ANOVA) test and Tukey's test showed that the time to first analgesic rescue was significantly prolonged in Group B as compared to Group A. Regarding VRS score at 4th and 6th post-operative hours Group B had lower pain scores as compared to group A. 2 patients (6.66%) in group A, 1 patient (3.33%) in group B had a sedation score of 1.28 patients (93.3%) in group A, 29 patients (96.6%) in Groups B had a sedation score of 2 as assessed using Ramsay sedation score. Heart rate, blood pressure, respiratory rate assessed at various time intervals showed no statistically significant differences. Episodes of hypotension and bradycardia were treated with inj. phentermine 6mg and inj. atropine 0.3mg respectively.

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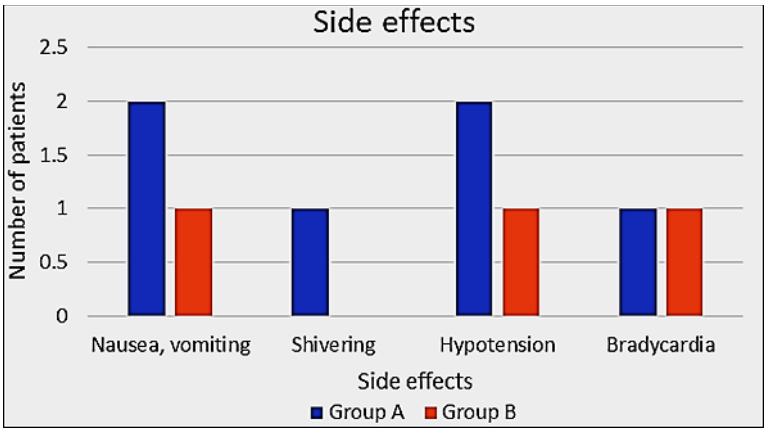

Fig 1: Incidence of side effects

Table 3: Demographic data (Mean ± S.D)

Parameter	Group A	Group B	P value
Age(years)	34.37 ± 9.01	35.16 ± 11.55	>0.05
Male	17	20	
Female	13	10	
ASA 1	27	28	
ASA 2	3	2	
Weight (kg)	58.93 ± 8.22	58.56 ± 8.7	
Height (cm)	165.30 ± 3.41	164.1 ± 4.38	

Table 4: Duration (Mean ± S.D)

	Time taken (minutes)		P value
	To reach T10 dermatome	For motor block to reach Bromage 3	
Group A	5.24±1.49	5.87 ± 0.3	p<0.01
Group B	3.57 ± 0.18	4.25 ± 0.47	

Discussion

Various adjuvants like epinephrine, phenylephrine, adenosine, magnesium sulphate, fentanyl, ketamine and clonidine have been used as adjuncts to local anaesthesia to avoid intraoperative visceral and somatic pain and to provide prolonged post-operative anaesthesia. But these adjuvants are associated with various side effects thereby limiting their use.Intrathecal α-2 adrenergic agonists have antinociceptive action for both somatic and visceral pain and can be used as adjuvants to local anaesthetics to potentiate the effects of local anaesthetics and allow a decrease in required dose without causing respiratory depression.Dexmedetomidine is an alpha-2 agonist and it was approved by Food and Drug Administration in 1999 for use in humans as a short-term medication for sedation/analgesia in the intensive care unit [4].

The mechanism by which intrathecal α-adrenoceptor agonists prolong the motor and sensory block of local anaesthetics is not well known. It may be an additive or synergistic effect secondary to the different mechanism of action of the local anaesthetic. The local anaesthetic acts by blocking sodium channels whereas α-adrenergic agonists are said to act by binding to pre-synaptic C-fibres and post-synaptic dorsal horn neurons. Their analgesic action is a result of depression of the release of C-fibre transmitters and hyperpolarisation of post-synaptic dorsal horn neurons and prolonged motor block might be caused by direct impairment of excitatory amino acids release from spinal interneurons [7]. A small intrathecal dose of

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dexmedetomidine (5 µg) used in combination with bupivacaine for spinal anaesthesia has been shown to produce a shorter onset of motor block and prolongation in the duration of motor and sensory block with hemodynamic stability and lack of sedation.Isolated perfused human placental studies have shown that dexmedetomidine transport into foetal circulation is very less. Due to the higher lipophilicity of dexmedetomidine, there is greater placental tissue retention and minimal transport into the foetal circulation [8]. In addition, dexmedetomidine has been safely used in neonates and infants for sedation in intensive care setups[9]. In this study, addition of dexmedetomidine (5 µg and 10 µg) to hyperbaric bupivacaine intrathecally produced a rapid onset of sensory and motor block, prolonged the sensory and motor block and the time to first analgesic requirement significantly in a dose dependent manner. It also maintained stable hemodynamic with minimal side effects. Results of the current study concur with the results obtained by Al-Ghanem SM *et al*.,who found that dexmedetomidine has a dose-dependent effect on the onset and regression of sensory and motor block and the time to rescue analgesia with lower Visual Analogue scores and minimal side effects when used as an adjuvant to spinal bupivacaine[10]. A study by Shukla D *et al*., concluded that there was no significant difference in the mean values of heart rate and mean arterial pressures between dexmedetomidine group (10 µg) and plain bupivacaine group. Administration of an α-2 agonist via an intrathecal or epidural route provides an analgesic effect without severe sedation. This effect is due to sparing of supraspinal central nervous system sites from excessive drug exposure, resulting in robust analgesia without heavy sedation[11].In present study there was no statistically significant differences in the sedation scores between three groups. The result of this study is in contrast to the result obtained by Sunil BV *et al*., who found that the sedation score was significantly higher in dexmedetomidine group (5 µg, 10 µg and 15 µg) as compared to plain bupivacaine group. The possible explanation was that they had premedicated all the patients with oral diazepam[12].

The main limitation of the study was that it involved only healthy adults and the effect in older patients with cardiovascular morbidities is not known. Secondly, total analgesic consumption in 24 hours was not noted.

Conclusion

On the basis of our study, we conclude that addition of dexmedetomidine to hyperbaric bupivacaine intrathecally produces a rapid onset of sensory and motor block prolongs the sensory and motor block and the time to first analgesic requirement significantly in a dose dependent manner together with stable hemodynamic parameters, and minimal side effects.

Conflicts of interest: Nil.

Acknowledgment: Nil.

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