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Original Research Paper

A COMPARISON BETWEEN THREE DIFFERENT DOSES OF INTRATHECAL DEXMEDETOMIDINE ADDED TO HYPERBARIC BUPIVACAINE FOR INFRA UMBILICAL SURGERIES

Anaesthesiology

KEYWORDS: Dexmedetomidine, Infra Umbilical Surgeries, Spinal Anaesthesia

Dr K Premakumari	Assistant Professor Department of Anaesthesiology Kanyakumari Government Medical College Asaripallam Nagercoil, Kanyakumari District Tamil Nadu, India Medical College Asaripallam Nagercoil, Kanyakumari District Tamil Nadu, India
Pratheeba Durairaj	Associate Professor Department of Anaesthesiology Kanyakumari Government Medical College Asaripallam Nagercoil, Kanyakumari District Tamil Nadu, India
Vasukinathan Arokyamuthu	Professor and Head of the Department Department of Anaesthesiology Kanyakumari Government Medical College Asaripallam Nagercoil, Kanyakumari DistrictTamil Nadu, India
Edward Johnson Joseph	Professor Department of Anaesthesiology Kanyakumari Government Medical College Asaripallam Nagercoil, Kanyakumari District Tamil Nadu, India

ABSTRACT

Background and goals of study: Spinal anesthesia using local anesthetics is associated with relatively short duration of action and hence early analgesic intervention is needed in post operative period. Adjuvants are added to improve the quality, to accelerate the onset of action and also to overcome the problems which occur during spinal analgesia. Alpha 2 adrenergic receptor agonist like dexmedetomidine gain the focus of interest for its sedative, analgesic, perioperative sympatholytic and hemodynamic stabilizing properties. Dexmedetomidine is a new highly selective drug among the alpha 2 adrenergic receptor agonist. This study is intended to compare three different doses of intrathecal dexmedetomidine added to hyperbaric bupivacaine for infra umbilical surgeries **Methods:** Sixty patients were grouped into three groups of twenty each in this randomised, prospective, parallel group, double-blinded study. Patients received 0.5% hyperbaric bupivacaine 2.4ml (12mg) + dexmedetomidine 5 µg, 10 µg or 15 µg in 0.6 ml normal saline. Intraoperative vital parameters, onset and level of sensory and motor blockade, duration of analgesia, postoperative sedation score and rescue analgesic requirement were observed.**Results:** The mean sensory blockade onset time of 5 µg group was significantly higher than the other two groups. The mean onset time of motor blockade of 15µg group was significantly lower than the other two groups. The duration of blockade and duration of analgesia were significantly higher in the 15µg group. Postoperative sedation score was significantly higher in the 15µg group. **Conclusion:** Intrathecal dexmedetomidine added to bupivacaine for lower abdominal surgeries, has a dose dependent effect on the sensory and motor blockade, with earlier onset and increased duration of blockade and prolonged post-operative analgesia, better level of sedation and stable hemodynamics.

INTRODUCTION: Spinal anesthesia using local anesthetics is associated with relatively short duration of action and hence early analgesic intervention is needed in post operative period. A common problem during infra umbilical surgery under spinal anesthesia is visceral pain, nausea and vomiting.

Adjuvants are added to improve the quality, to accelerate the onset of action and also to overcome the problems which occur during spinal analgesia. Adrenaline was the first spinal adjuvant used. Adrenaline reduces its toxicity but does not greatly prolong its effect.

Various adjuvants like morphine, fentanyl, sufentanil, clonidine, midazolam, ketamine, neostigmine, sodabicarbonateare added to local anesthetics and the latest inclusion is dexmedetomidine[1]. Adjuvants are administered by various routes like epidural, intrathecal and intravenous. In our study adjuvant is added to local anesthesic through intrathecal route.

Alpha 2 adrenergic receptor agonist like dexmedetomidine gain the focus of interest for its sedative, analgesic, perioperative sympatholytic and hemodynamic stabilizing properties. Dexmedetomidine is a new highly selective drug among the alpha 2 adrenergic receptor agonist. It has been approved by FOOD AND DRUGS ADMINISTRATION for short term sedation for mechanically ventilated ICU patients. No neurological defects have been reported till date in both human and animal studies during intrathecal use. This study is intended to compare three different doses of intrathecal dexmedetomidine added to hyperbaric bupivacaine for infra umbilical surgeries (Unilateral Inguinal Hernia surgeries and Vaginal Hysterectomies)

METHODOLOGY:

This is a randomised, prospective, parallel group, double-blinded study. Simple randomised sampling was done by computer generated random numbers. Sixty patients were studied. ASA I and II patients between 18-60 years of both sexes undergoing Elective surgeries (Inguinal herniorrhaphy and Vaginal hysterectomies) were included in the study. Patients with known hypersensitivity to any of study drugs, those with known contra indication to Regional Anesthesia, those with known or suspected coagulopathy, and those with renal disorders hypertension, IHD, heart blocks, arrhythmias and cardiac valvular abnormalities, patients on blockers, patients on any long term analgesic therapy, and patients on medications known to interact with study drugs were excluded from the study.

After obtaining Institutional Research and Ethical Committee (TIREC) approval and written informed consent, the patients were randomly allocated into three groups.

Group A (n=20) patients received 0.5% hyperbaric bupivacaine 2.4ml (12mg) + dexmedetomidine 5 µg in 0.6 ml normal saline.
Group B (n=20) patients received 0.5% hyperbaric bupivacaine 2.4ml (12mg) + dexmedetomidine 10 µg in 0.6 ml normal saline.
Group C (n=20) patients received 0.5% hyperbaric bupivacaine 2.4ml (12mg) + dexmedetomidine 15 µg in 0.6 ml normal saline.

The anesthesiologist who administered the drug and the observer were blinded to the study. Sterile syringes containing 3.0 ml of the total volume of the drug were loaded by another anesthesiologist not participating in the study. The intraoperative monitoring and postoperative observation was done by the same anesthesiologist who administered the drug, but was unaware of the content of the

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syringes.

Emergency drugs and equipments were kept ready. Pre-loading done with 20 ml/kg of intravenous infusion of Ringer lactate. Monitors were connected to the patients and baseline values of heart rate, systolic, diastolic and mean arterial pressures, and oxygen saturation were noted.

Under strict aseptic precaution the sub-arachnoid block was done approaching through L3-L4 interspace with a 26 gauge quincke's needle. After confirming free flow of CSF, the drug was injected according to the group assigned. After injecting the drug, the patients were turned to supine position. When the peak level of sensory block is reached, the surgeon was instructed to proceed.

Pulse rate, systolic blood pressure, mean blood pressure, diastolic blood pressure, respiratory rate, SPO2 were recorded before starting procedure and thereafter 5, 10, 15, 20 minutes interval till the end of the surgery and thereafter at hourly second and fourth hourly interval till 24 hours. Hypotension was defined as systolic blood pressure less than 90mm Hg or decrease in MAP below 20%of the baseline value. Hypotension, if any occurred was treated with Inj.Ephedrine (6mg) incremental boluses.

Sensory blockade was assessed by pin prick with a short hypodermic needle at 1 minute interval until the block reached T10 level and the maximum height of the sensory block was noted at 20 minutes. Onset of sensory blockade was defined as the time taken from the drug injection to the time to reach T10 level and the offset of sensory block was presumed when pin prick sensation at S1 dermatome has returned. Duration of sensory block was defined as the time interval elapsed between onset of sensory block at T10 to regression of sensory block to S1.

Motor blockade was assessed using Modified Bromage score at 1 minute interval until complete motor block occurred. Onset of motor block was defined as the time taken from the injection of drug to the development of complete motor blockade, i.e., Bromage score-3. Complete recovery from motor block was defined as attaining Bromage score-0 and the duration of motor block means that the time taken from the onset of complete motor blockade to complete recovery of motor block.

Pain was evaluated using Visual Analogue Scale. Inj. Diclofenac 75mg was administered intra-muscularly as a rescue analgesic when the pain score crossed a score of 4.

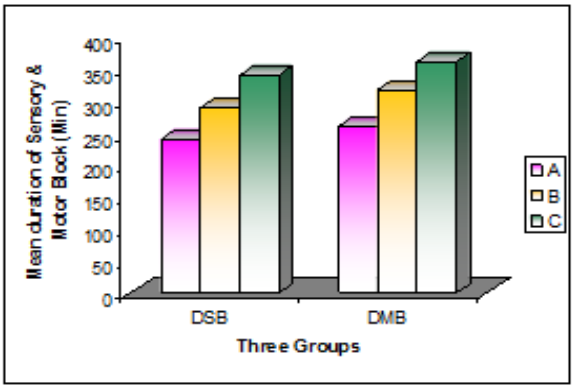
Duration of Analgesia was assessed as the period from the time of subarachnoid block to the time when the patient needs the first dose of rescue analgesic drug. Sedation was assessed using Ramsay Sedation Score. Post operatively the patients were followed for upto 24 hrs for any adverse effects like nausea, vomiting, pruritus, respiratory depression, any neurological complications and urinary retention.

RESULTS:

The three groups were matched according to their age for randomization and found that there was no difference between the mean ages between them (44.4 ± 10.7 ≈46.0±5.6 ≈ 44.4±8.1 and P>0.05). The mean pre-op pulse rate, SBP, MAP, SPO2 and duration of surgery were matched and found that no significant differences were observed between the three groups (P>0.05). The mean sensory blockade onset time of A group was significantly higher than the other two groups B&C (A>B&C; 226.1±28.7 > 206.8±20.2 & 197.2±14.9 and P<0.05). The mean values of B& C groups were approximately equal (206.8±20.2 ≈ 197.2±14.9 and P>0.05). The mean onset time of motor blockade of C group was significantly lower than the other two groups (190.4±14.2< 233.0±23.3 & 228.2±16.8 and P<.001). The onset time for motor block of the other two groups namely A and B were not significant (233.0±23.3 ≈ 228.2±16.8 and P>0.05).

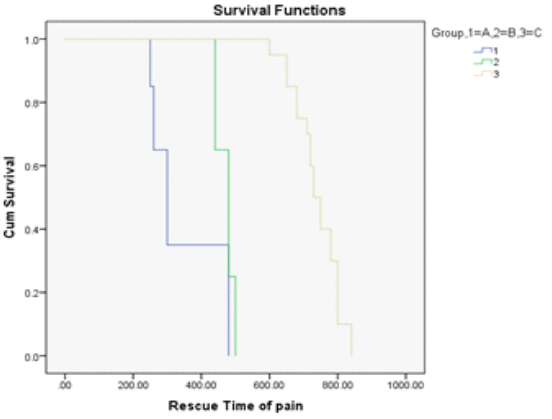
The highest sensory level achieved for A group was T6 and C group was T4. Among the A&B group subjects, 65% and 40% were associated with T8 sensory level and among the C group subjects 40% were associated with T4 sensory level. The above levels were statistically very highly significant (P<0.001).

The mean pulse rates, mean SBP, mean MAP and mean SPO2 between the three groups are not significantly different (P>0.05). The duration of sensory block of C group was significantly longer than B and B group was significantly longer than A group (341.5±47.6>290±56.2>241.0 ±48.9 and P<0.001). Similarly the duration of motor block of C group was significantly longer than B and B group was significantly longer than A group (362.5±16.5>318.0 ±31.0>260.6±41.5 and P<0.001).



The two segment regression times between three groups were 139.7±28.2, 143.2±28.8 and 172.7±30.2.minutes respectively. The group C regression time was significantly greater than the other two groups (172.7±30.2.> 143.2±28.8 &139.7±28.2, and P<0.00). But the regression times between the groups A and B was not significant (143.2±28.8 ≈139.7±28.2 and P<0.05). The mean duration of analgesia of C group was significantly longer than the B group and B group was significantly longer than A group (740.5±65.9>471.0±24.6>347.5± 101.4 and P<0.001).

Comparison of Analgesia survival functions between three groups. (Kaplan Meier Survival function curve):



The above curve explains the time of analgesia from the starting of anesthesia to the onset of VAS pain score 4. The range of group A was 250 to 480 minutes, B group was 440 to 500 and C group was 600 to 840 minutes.

The highest sedation score achieved for A group was 2 and C group was 4. The C group achieved more sedation levels wherein 55% reached score 3 and 45% reached score 4. The above levels were statistically very highly significant (P<0.001).

Bradycardia and Hypotension were the only adverse effects noted, and was much associated with the C group. But the association

within the groups did not have any statistical significance (P>0.05).

DISCUSSION:

Recent researches have revealed that the administration of an 2-agonist in the centro-neuraxial blockade produces prolonged postoperative pain relief without undue sedation. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in analgesia without heavy sedation. The mechanism by which intrathecal α_2-adrenergic agonists prolong the motor and sensory block of local anesthetics is still not clearly understood. Intrathecal α_2-adrenergic agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. This anti-nociceptive effect may explain the prolongation of the sensory block when added to spinal anaesthetics. The prolongation of the motor block of spinal anaesthetics may result from the binding of $_2$-adrenergic agonists to motor neurons in the dorsal horn.

Most of the clinical experience gained in the use of intrathecal $_2$-adrenoceptor agonists has been described with clonidine, which has a potent synergistic effect with local anaesthetics. There are only few research available using a combination of intrathecal dexmedetomidine and local anaesthetics. The dose of epidural/ caudal dexmedetomidine reported is in the range of 1.5 - 2 μg/kg[2]. Compared with clonidine, dexmedetomidine has 10 times higher receptor binding affinity. Extrapolations led to the calculation of an equipotent dose of intra-thecally administered dexmedetomidine. Several clinical studies have established that intrathecal clonidine increases the duration of sensory and motor spinal block when added to spinal local anaesthetics and this effect of clonidine is dose-dependent[3]. Doses of more than 75 g are accompanied by excessive sedation, hypotension and bradycardia. Intrathecal dexmedetomidine upto 10μg added to local anaesthetics has not produced any major adverse effects during the studies conducted by these authors discussed above. *De kocket al*[3] recommended a dose of 15-45 g clonidine for supplementation of spinal anesthesia which effectively prolongs the duration of spinal block with minimal sedation and side effects. Higher intrathecal doses of clonidine have been tried. But there is no published literature for intrathecal doses of more than 10μg of dexmedetomidine. The equipotent dose for 5, 10 and 15μg of dexmedetomidine when compared to clonidine would approximate 50, 100 and 150μg respectively.

Kanazi et al[4], who pioneered using dexmedetomidine in humans for spinal anesthesia, hypothesized that intrathecal dexmedetomidine 3 μg or clonidine 30 μg would be equipotent and would produce a similar effect on the characteristics of bupivacaine spinal anesthesia. These conclusions were arrived, pondering over previous animal studies using intrathecal dexmedetomidine. The authors added a low dose of 3 μg of dexmedetomidine or 30 μg of clonidine to 12 mg of intrathecal bupivacaine. They found no significant difference between the groups with respect to blockade characteristics, analgesia and sedation. They confirmed their hypothesis that the intrathecal doses of dexmedetomidine and clonidine used in the study are equipotent. *Al-Mustafa et al*[5] hypothesized that 5 μg and 10 μg of intrathecal dexmedetomidine might be equipotent to 50 μg and 100 μg of intrathecal clonidine respectively. They administered dexmedetomidine intrathecally along with bupivacaine to a maximum dose of 10μg. They observed that dexmedetomidine had a dose dependant effect on the onset and regression of sensory and motor block when used as an adjuvant to bupivacaine in spinal anesthesia. *Ashraf Amin Mohamed et al*[6], compared 5μg dexmedetomidine with 25μg fentanyl added to bupivacaine for abdominal surgeries. They observed that intrathecal 5 g dexmedetomidine improved the quality and the duration of postoperative analgesia. In another similar study, *Subhi Al-Ghanemet al*[7] compared the effect of adding 5μg dexmedetomidine versus 25μg fentanyl to intrathecal bupivacaine in vaginal hysterectomies. They concluded that 10 mg plain bupivacaine supplemented with 5 μgdexmetedomidine produces prolonged motor and sensory block compared with 25 g fentanyl. *Gupta et al*[8], from their study, concluded that 5μg dexmedetomidine added to ropivacaine intrathecally produces a prolongation in the duration of the motor and sensory block. *Shukla et al*[9], compared 10μg of intrathecal dexmedetomidine to magnesium sulphate as adjuvants to bupivacaine, and concluded that dexmedetomidine provided earlier onset and prolonged duration of sensory and motor blockade, without any significant hemodynamic alterations.

In the present study, we observed that the onset time of sensory and motor blockade was dose dependent. Group A (226.1±28.7 seconds) significantly differed (P<0.001) with group B (197.2±14.9 seconds) & C (206.8±20.2 seconds) in respect of their sensory on set time. This means that the onset of sensory blockade was earlier with higher doses. The onset time of motor block was also earlier with increasing doses. Group C (190.4±14.2 seconds) significantly differed (P<0.001) with group A (233.0±23.3 seconds) & group B (228.2±16.8 seconds). A dose related increase in the level of sensory blockade (C>B>A) was noted. The duration of sensory and motor blocks between the groups was also dose dependent, and significantly (P<0.001) differed from each other. The duration of both sensory and motor blockade was highest with group C (sensory mean-341.5±47.6 minutes, motor mean-362.5±16.5 minutes). The 2 segment regression time was highest with group C (mean-172.7±30.2 mins). The mean duration of analgesia was dose dependent with C>B>A (740.5 ±65.9>471.0±24.6> 347.5± 101.4 minutes; P<0.001). The post-operative sedation was also dose dependent with group C exhibiting a minimum score of 3 and maximum of score 4. None of the patient showed signs of respiratory depression.

From the present study, it is clear that intrathecal dexmedetomidine with spinal bupivacaine not only shortens the onset of anesthesia, but also prolongs the duration of blockade and achieves longer duration of analgesia. Adverse effects pertained to opioid administration, such as nausea, vomiting, pruritus and urinary retention were not noted in any of the patient. Bradycardia and hypotension occurred in 10 out of 60 patients, with group C>B>A (5, 3 and 2 respectively), but were not statistically significant. Bradycardia required no treatment, and correction of hypotension required less than 12-18 mg of ephedrine in incremental boluses. Otherwise the patients remained hemodynamically throughout. The statistical analysis of the pre, intra and post-op hemodynamic variables such as PR, SBP, MAP and SPO_2 between the three groups showed no statistically significant hemodynamic fluctuation. The results of the present study, when compared to the studies of the authors discussed above, have similar outcome with respect to the onset and duration of sensory and motor block, the duration of analgesia and hemodynamic profile.

CONCLUSION:

Intrathecal dexmedetomidine added to bupivacaine for lower abdominal surgeries, has a dose dependent effect on the sensory and motor blockade, with earlier onset and increased duration of blockade and prolonged post-operative analgesia, better level of sedation and stable hemodynamics.

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