Original Research Article

Comparison of intrathecal dexmedetomidine - 0.5% heavy bupivacaine combination with intrathecal 0.5% heavy bupivacaine alone for lower limb and lower abdominal surgeries

Deoshri Bal Ramteke[1], Surekha Shinde[2*]

[1]Assistant Professor, Department of Anaesthesia, Grant Government Medical College and Hospital, Mumbai, Maharashtra, INDIA.
[2]Associate Professor, Department of Anaesthesia, Dr. V. M. Medical College Solapur, Maharashtra, INDIA.
Email: deoshri02@gmail.com

Abstract

Aims: To assess the effects of intrathecal dexmedetomidine on the onset and duration of action of sensory and motor block, haemodynamic alteration, associated complications, level of sedation and intraoperative analgesia. **Methods:** The study consists of 100 patients scheduled for lower abdominal and lower limb surgeries. Patients were randomly allocated in 2 groups. Group -1 received 0.5% Hyperbaric bupivacaine 3cc (15 mg) and Group-2: received 0.5% hyperbaric bupivacaine (15mg) + 5ug Dexmedetomidine. Time of onset of sensory blockade, maximum level of sensory blockade, time to achieve maximum level of sensory blockade, and maximum level of motor blockade, duration of maximum motor blockade, time for segment regression of Sensory blockade, total duration of analgesia and sedation, and incidence of side effects were recorded. **Result:** Mean duration of onset of sensory blockade to level T10 with Group 1 was 9.70±1.23minute while it was 6.84±0.93 minutes with Group2. Mean duration of onset of maximum sensory blockade to level T6 in Group was 18.86 ± 1.77 minute while it was 17.30 ± 1.88 minute with Group 2. Mean duration of onset of maximum motor blockade to bromage 3 with Group 1 was 21.86 ± 1.68 minute while it was 13.12 ± 1.00 minute with Group 2. Mean duration of segment regression of sensory blockade to level S1 segment prolonged in Group 2. (Group 1-170.24 ± 10.53 minute while it was 296.90 ± 22.24minute with Group 2) (p-value<0.001). Mean duration of regression of motor blockade to bromage 0 with group 1 was 147.02 ± 9.58minute while it was 254.60 ± 13.99 minute with group 2. Duration of analgesia was measured as time interval between intrathecal injection to patients 1st request of analgesic. It was prolonged in group 2. (Group 1 -184.52 ± 13.83 minute, Group 2 -344.60 ± 31.51minute). There is no significant difference between mean heart rate and MAP in group 1 and group 2. Sedation was assessed by Ramsays sedation score graded from 1 to 6 depending upon whether patient is awake or in deep sleep. Sedition in patients in whom dexmedetomidine was used was comparatively more than with bupivacaine alone. There no significant difference of side effects in group 1 and group 2. **Conclusion:** Addition of dexmedetomidine to intrathecal bupivacaine produced significantly fast onset of sensory and motor block as well as significantly longer duration of sensory and motor block than bupivacaine alone without serious side effects

Key Words: Dexmeditomidine, bupivacaine.

[*]**Address for Correspondence:**
Dr. Surekha Shinde, Associate Professor, Department of Anaesthesia, Dr. V. M. Medical College Solapur, Maharashtra, INDIA.
Email: deoshri02@gmail.com
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Subarachnoid blockade with local anaesthetics provide intense analgesia by segmental blockade of central neural axis. But the duration is short lasting. Various drugs are administered intrathecally along with local anaesthetics to prolong the duration of action in post-operative period viz. adrenaline, neostigmine, opioids, morphine, pethidine, pentazocine, methadone, tramadol, fentanyl, sufentanil, neostigmine, midazolam, adenosine, clonidine but each has its advantages and disadvantages, limiting

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their use. Like other adjuvats, dexmedetomidine intrathically was studied to prolong the sensory and motar blockade and post operative analgesia. Dexmedetomidine is a more selective α2 agonist with a 1600 greater selectivity for the α2 receptor compared with the α1 receptor. Three subtypes of α2 adrenoreceptors have been described in humans: α2A, α2B, and α2C. The α2A adrenoreceptors are primarily distributed in the periphery, whereas α2B and α2C are in the brain and spinal cord. Postsynaptic located α2 adrenoreceptors in peripheral blood vessels produce vasoconstriction, whereas presynaptic α2 adrenoreceptors inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. The overall response to α2 adrenoreceptors agonists is related to the stimulation of α2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociception effects of α2 adrenoreceptors.[1] It was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients. Dexmedetomidine is now being used off-label outside of the ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units, and for other applications such as withdrawal/detoxification amelioration in adult and pediatric patients. In present study, we tried to study analgesic effectiveness of intrathecal Dexmedetomidine-0.5% heavy bupivacaine combination with intrathecal 0.5% heavy bupivacaine alone for lower limb and lower abdominal surgeries. We also studied the onset and duration of motor andsensory blockage and its effects on post operative analgesia, haemodynamic alteration and associated complications.

MATERIAL AND METHODS

This study was a prospective, randomised double-blind, controlled, single centre study. The study was conducted in a Tertiary care level institute and a clinical research organization. A synopsis of the study protocol was submitted to the Institutional Review Board/Ethics committee and approval was obtained. After discussion on the study proposal, necessary permission was obtained from the Head, Department of Anaesthesia at the concerned tertiary care institute. Patients were examined one day prior to surgery and baseline recordings of pulse, blood pressure and other vitals were recorded. Informed written consent was obtained from the patients prior to joining the study. The study consists of 100 patients in the age group 18-55 yrs, weight 45 -75 kg, belonging to ASA grade I and II scheduled for lower abdominal and lower limb surgeries. Ptatients were randomally allocated in 2 groups. Each group consisted of 50 patients.

Group 1: Control group: Received 0.5% Hyperbaric bupivacaine 3cc (15 mg)

Group 2: Received 0.5% hyperbaric bupivacaine (15mg) + 5 ug Dexmedetomidine.

Patient having heart disease (using ά2 adrenergic receptor antagonist, calcium channel blockers, Angiotensin converting enzyme inhibitors), dysarrythmias on ECG, respiratory disease,, renal, hepatic disease, Diabetes mellitus, metabolic disorder,, diseases of CNS,, bleeding disorders, local infection of spinal area were excluded from study. Patients under study were subjected to thorough preoperative assessment including detailed case history, clinical examination and all necessary investigations. A written, informed and valid consent was taken from all the patients after explaining the procedure and its consequences. In operation theatre I/V cannula was inserted. Patient received no premedication. Monitors were attached (NIBP, Spo2,ECG). Preloading was done with Ringer Lactate (RL) solution (10ml/kg). In sitting position, parts prepared, painted and drapped. Under all aseptic precautions L3-L4 space palpated. Lumbar puncture was done with No. 25 G spinal needle and free, clear flow of CSF was obtained. Subarachnoid space was confirmed by aspirating CSF. Inj. Bupivacaine 0.5% heavy alone or Inj. Bupivacaine 0.5% heavy + Inj. Dexmedetomidine was injected into subarachnoid space according to the group alloted to them. Supine position was given immediately.O2 by ventimask @ 4-6 lit/min. Motor and Sensory block was assessed every minute. Motor block was assessed by asking the subject to lift his lower limbs. Complete motor block is when no voluntary movement is possible. Sensory block was assessed by a pin prick test performed with 22 G short bore needle. During surgery, patient did not receive any sedation. IV fluids were administered perioperatively dictated by blood loss and hemodynamic instability. Baseline observation were started before intrathecal drug injection. Heart rate, NIBP, ECG and peripheral Oxygen saturation (SPO2) were monitored intraoperatively. After intrathecal drug injection, data was recorded during 1st hr. at 15, 30, 45, 60 minutes and there after every hour up to l8 hrs followed by 4 hrly interval upto 24 hours. Sensory level of anaesthesia was assessed by pin prick test. Duration of anaesthesia was measured as the time interval from intrathecal injection to regression of sensory block below L1. Assessment of pain was done using “Visual Analogue Scale” between 0-10. 0: NO pain: 10-most severe pain Grade VAS Analgesia (0-1 Good analgesia, 1-4 Moderate analgesia, 4-7 Mild analgesia, 7-10 No analgesia). Supplement analgesia was administered when VAS > 3, Inj. Diclofenac 75mg i/m. Sedation was judged

by "Ramsay Sedation Scale" Score[2] Level of Sedation (1. Anxious or agitated or restless or both, 2. Co-operative, oriented and tranquil, 3. Responding to commands only, 4. Brisk response to light Glabellar tap, 5.Sluggish response to light Glabellar tap. 6.No response to light Glabellar tap.) Motor block was assessed according to "Modified Bromage Scale"[3] (Bromage 0: Patient able to move hip, knee and ankle; Bromage1: Patient unable to move hip but able to move knee and ankle; Bromage 2: Patient unable to move hip and knee but able to move ankle; Bromage 3: Patient unable to move hip, knee and ankle.) Patients were monitored for occurrence of side effects and complications during intra operative and post operative period. (Hypotension, bradycardia, nausea, vomiting). Parameters studied and compared were time of onset of sensory blockade, maximum level of sensory blockade, time to achieve maximum level of sensory blockade, and maximum level of motor blockade, duration of maximum motor blockade, time for segment regression of Sensory blockade, total duration of analgesia and sedation, and incidence of side effects. The detailed data was entered into well tabulated Microsoft Excel sheet and subsequently analyzed statistically. Data were expressed as mean ± SD. Sample t test was used depending upon the nature of data. Graphical display was done for visual inspection. Sedation assessed by mann whitney U test, Incidence were compared using chi square test. p-value < 0.05 was considered significant.

RESULTS

In study 100 patient were divided into two groups of 50 each. Group 1 received 0.5%hyperbaric bupivacaine 3ml (15mg) intrathecally. Group 2 received 0.5%hyperbaric bupivacaine 3ml (15mg) and 5µg dexmedetomidine intrathecally. These groups were comparable with respect to their physical parameters like age, height and weight. Duration of surgery and sex ratio in 2 groups was also comparable. (Table 1) There was no significant difference in pulse rate or systolic and diastolic blood pressure before induction in each group. Onset of sensory blockade to T10 and motor blockade to bromage 3 was statistically significant. Statistically significant difference was observed in duration of action of spinal anesthesia, time to regression of sensory blockade to S1, time to regression of motar blockade to bromage 0, duration of post operative analgesia and sedation. (Table 2). Mean duration of onset of sensory blockade to level T10 with Group 1 was 9.70±1.23minute while it was 6.84±0.93 minutes with Group2. By using 2 independent sample t-test p-value < 0.05 significant difference between mean onset of sensory blockade in group 1 and group 2.(p-value < 0.001).Mean duration of onset of maximum sensory blockade to level T6 in Group was 18.86 ± 1.77 minute while it was 17.30 ± 1.88 minute with Group 2. By using 2 independent sample t-test p-value < 0.05 therefore there is significant difference with between mean time to achieve the T6 of sensory blocked in group 1 and group. (p-value<0.001). Mean duration of onset of maximum motor blockade to bromage 3 with Group 1 was 21.86 ± 1.68 minute while it was 13.12 ± 1.00 minute with Group 2. Mean duration of segment regression of sensory blockade to level S1 segment prolonged in Group 2. (Group 1-170.24 ± 10.53 minute while it was 296.90 ± 22.24minute with Group 2) (p-value <0.001). Mean duration of regression of motor blockade to bromage 0 with intrathecal injection of 3cc 0.5% hyperbaric bupivacaine was 147.02 ± 9.58minute while it was 254.60 ± 13.99 minute with intrathecal injection of 3cc 0.5% hyperbaric bupivacaine and 5µg dexmedetomidine. Duration of analgesia was measured as time interval between intrathecal injection to patients 1st request of analgesic. It was prolonged in group 2. (Group 1 -184.52 ± 13.83 minute, Group 2 -344.60 ± 31.51minute). There was no significant difference between mean heart rate and MAP in group 1 and group 2. (figure1 and 2) Sedation was assessed by Ramsays sedation score graded from 1 to 6 depending upon whether patient is awake or in deep sleep. Sedition in patients in whom dexmedetomidine was used was comparatively more than with bupivacaine alone. Median sedation score was 2 in both group1 and group2. By using Mann Whitney U test p-value < 0.05 therefore there is significant difference between sedation score in group 1 and group 2.(p-value< 0.001). The incidence of hypotension was more in Group 2. 3 patients out of 50 in Group 2 where as incidence is 2 out of 50 patients in Group 1 alone. Similaraly incidence of bradycardia more with Group 2, 2 patient out of 50 where as incidence is 1 out of 50 patients with Group 1. Nausea occur only in 1 patient with Group 2. There was no incidence of vomiting in both group. By using chi-square test there no significant difference of side effects in group 1 and group 2.(Table 3).

Table 1: Descriptive Statistics

	Group 1	Group 2	P value
Gender Male	26	29	0.861
Female	24	21	
Age(yrs)	39.36±7.80	39.20±8.08	0.920
Height(cm)	161.52±7.55	159.06±6.83	0.091
Weight(kg)	61.54±7.13	60.18±6.89	0.334
Duration of surgery(min)	104.90±14.30	107.00±14.46	0.467

Table 2

	Group 1	Group 2	P value
onset of sensory blockadeT10(min)	9.70±1.23	6.84±0.93	<0.001
time to achieve the T6 of sensory blocked	18.86±1.77	17.30±1.88	<0.001
Mean duration of onset of maximum motor blockade to bromage 3(min)	21.86±1.68	13.12±1.00	<0.001
Mean duration of segment regression of sensory blockade to level S1(min)	170.24±10.53	296.90±22.24	<0.001
Mean duration of regression of motor blockade to bromage 0(min)	147.02±9.58	254.60±13.99	<0.001
Duration of analgesia(min)	184.52±13.83	344.60±31.51	<0.001

Table 3: Comparision of side effects

	Number of patients		
	Group 1 (n= 50)	Group 2 (n= 50)	p-value
Hypotension	2 (4.0%)	3 (6.0%)	0.999
Bradycardia	1 (2.0%)	2 (4.0%)	0.999
Nausea	0	1 (2.0%)	0.999
Vomiting	0	0	-

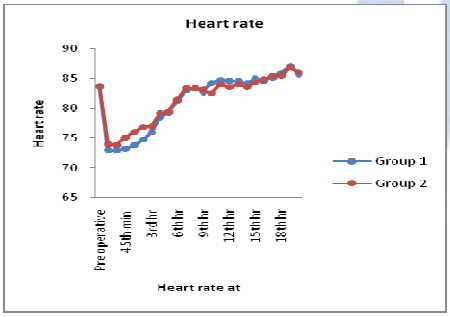

Figure 1: There was no significant difference between mean HR in group 1 and group 2

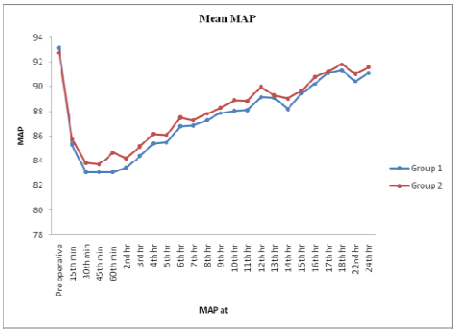

Figure 2: There was no significant difference between mean MAP in group 1 and

DISCUSSION

Pain in the post-operative period is associated with various systemic side effects including respiratory, cardiovascular and other systems, which increases the morbidity and mortality. Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and nonopioid) analgesics and regional (i.e., neuraxial and peripheral) analgesic techniques. Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain. These agents generally exert their analgesic effects through μ-receptors in the CNS, although there is evidence that opioids may also act at peripheral opioid receptors. A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Realistically, the analgesic efficacy of opioids is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation, or respiratory depression. Spinal anaesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. But 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, midazolam, fentanyl and others are studied to prolong the effect spinal anaesthesia. Dexmedetomidine is the d-enantiomer of medetomidine, a substance that has been used for sedation and analgesia in veterinary medicine for many years.[4] It shows a high ratio of specificity for the α2 receptor (α2/α1 1600:1) compared with clonidine (α2/α1 200:1), making it a complete α2 agonist.[5] Animal studies conducted in rats, rabbits, dogs and sheep have used intrathecal dexmedetomidine at a dose range of 2.5-100 mg[6-13]. The largest dose of intrathecal dexmedetomidine, 100 mg, was used in a sheep model, where a 7-day follow-up showed no neurological deficits in the studied animals. In humans, the dose of epidural dexmedetomidine reported is in the range of 1.5—2 mg/kg. Fukushima *et al*.[14] administered 2 mg/kg epidural dexmedetomidine for post-operative analgesia in humans without any reports of neurological deficits. Maroof *et al*.[15] used epidural dexmedetomidine, approximately 1.5 mg/kg, to decrease the incidence of post-operative shivering without any reports of neurological deficits. In our study no neurological deficit was found. The local anaestetics acts by blocking sodium channels and α2 adreno receptor agonist acts by binding to presynaptic C fibres and post synaptic dorsal horn neurons. Intrathecal dexmedetomidine when combined with spinal bupivacaine prolongs the sensory block by depressing the release of C-fibers transmitters and by hyperpolarization of post-synaptic dorsal horn neurons[16-20]. Motor block

prolongation by 2-adrenoreceptor agonists may result from binding these agonists to motor neurons in the dorsal horn of the spinal cord[21-22]. Intrathecal α2-receptor agonists have been found to have antinoniceptive action for both somatic and visceral pain. The analgesic effects of dexmedetomidine are complex. Alpha2 agonists do have an analgesic effect when injected via the intrathecal or epidural route.[23] Intrathecally injected dexmedetomidine in sheep reduces blood pressure in 1 minute. When dexmedetomidine is injected into the epidural space, it rapidly diffuses into the CSF (in one study,[24] 22% of the injected dose was identified in the CSF). The effects on blood pressure are slower in onset with an epidural injection than with an intrathecal administration. Epidural effects are seen in 5 to 20 minutes. The primary site of analgesic action is thought to be the spinal cord.[24] In our study, in dose of 5 µg dexmedetomidine 3 patient out of 50 had an hypotension. G.E. Kanazi, M.T[25] studied effect of low dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. They compare the onset and duration of sensory and motor block, as well as the hemodynamic changes and level of sedation, following intrathecal bupivacaine supplemented with either dexmedetomidine or clonidine. Kanazi *et al*. found that 3 µg DXM and 30µg clonidine are equipotent intrathecally when added to bupivacaine in patients undergoing urology procedures. They found that dexmedetomidine and clonidine produced significantly fast onset of sensory and motor block as well as significantly longer duration of sensory and motor block than bupivacaine alone without serious side effects. In our study we also found that dexmedetomidine produced significantly fast onset of sensory and motor block as well as significantly longer duration of sensory and motor block than bupivacaine alone without serious side effects. In 2009, Mahmoud M. Al Mustafa[26] studied the effect of dexmedetomidine added to spinal bupivacaine for urological procedure. They concluded that dexmedetomidine has dose dependant effect on onset and regression of sensory and motar block used as adjuvant to bupivacaine in spinal anaesthesia. In2011,Rajni Gupta *et al*,[27] done a comparative study of intrathecal dexmedetomidine and fentanyl as adjuvant to bupivacaine for lower abdominal surgeries. Patients were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine plus 5 µg dexmedetomidine (group D, n = 30) or 12.5 mg hyperbaric bupivacaine plus 25µg fentanyl (group F, n = 30) intrathecal. They found that patients in dexmedetomidine group (D) had a significantly longer sensory and motor block time than patients in fentanyl. Rajani Gupta[27] uses a dexmedetomidine as an intrathecal adjuvant for postoperative analgesia in randomised double blind trial. Sixty patient randomly allocated to receive intrathecally either 3ml 0.75% isobaric ropivacaine + 0.5ml normal saline(group R0 or 3ml of 0.75% isobaric ropivacaine + 5µg dexmedetomidine in 0.5ml normal saline. They found that addition of dexmedetomidine to ropivacaine intrathecally produces a prolongation in the duration of motor and sensory block. In our study sedation was assessed by Ramsays sedation score graded from 1 to 6 depending upon whether patient is awake or in deep sleep. Sedition in patients in whom dexmedetomidine was used was comparatively more than with bupivacaine alone. Median sedation score was 2 in both group1 and group 2. Duration of analgesia significantly more when dexmedetomidine is added to bupivacaine. Mild sedation is observed with dexmedetomidine. Sedation score was not more than 3 in any of these patients, none of these patients were deeply sedated or associated with respiratory depression in our dose. The occurrence of side effects like hypotension, bradycardia, nausea were more in patients with dexmedetomidine group as compared to bupivacaine alone but not statistically significant. The overall incidence of side effects is less. Heart rate and mean arterial pressure does not decrease significantly intra operatively and post operatively with 5µg dexmedetomidine.

CONCLUSION

Thus dexmedetomidine is a good adjuvant drug and its use intrathecally as an additive to bupivacaine does extend the duration of spinal anesthesia significantly, lowering the need to administer general anesthesia if duration of surgery is prolonged. Further it also provides excellent post operative analgesia. The drawback of intrathecal dexmedetomidine is increase in duration of motor blockade which may not be suitable for short duration of surgeries. In conclusion, 5µg dexmedetomidine seems to be an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures of prolonged duration with minimal side effects and excellent quality of spinal analgesia.

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