

## A RANDOMIZED CONTROLLED DOUBLE-BLINDED PROSPECTIVE STUDY OF THE EFFICACY OF LOW DOSE OF DEXMEDETOMIDINE AS AN ADJUVANT TO INTRATHECAL BUPIVACAINE IN HYSTERECTOMIES

Sangeeta Agarwal Bansal<sup>1</sup>, Vinita Agarwal Bansal<sup>2</sup>

<sup>1</sup> Department of Anesthesiology, Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, India

<sup>2</sup> Department of Obstetrics and Gynecology, Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, India

Correspondence to: Sangeeta Agarwal Bansal (sagarwal2111@gmail.com)

DOI: 10.5455/ijmsph.2014.140420143

Received Date: 27.03.2014

Accepted Date: 14.04.2014

### ABSTRACT

**Background:** Hysterectomies are the surgeries which are associated with visceral and somatic pain. To prolong sensory block and get good perioperative analgesia, various adjuvants are under trial.

**Aims & Objective:** To study the effects of low dose of intrathecal Dexmedetomidine as adjuvant to Bupivacaine in hysterectomies.

**Materials and Methods:** This was a prospective randomized double blind control study. Sixty patients were randomly allocated into two groups to receive intrathecal either 3.5 ml of 0.5 % hyperbaric Bupivacaine + 0.5 ml normal saline in Group I, or 3.5 ml of 0.5% hyperbaric Bupivacaine + 0.5ml of 5 µg Dexmedetomidine in Group II. Demographic data, haemodynamic, onset and duration of sensory and motor block and other side effects were analyzed. Statistical analysis was done by using f test and t test in data analysis add in package of the Microsoft Excel.

**Results:** Two groups were comparable with respect to demographic data. Onset of sensory block at T10 level was comparable in both groups. However the onset of motor block was found early in Group II (P value 0.006). There was significant prolongation of duration of sensory and motor block found in group II. For sensory block (P value:  $0.0018 \times 10^{-8}$ ) and motor block (P value:  $0.002 \times 10^{-6}$ ). Haemodynamic, nausea, vomiting, shivering data findings were comparable. There was significant sedation found in Group II (P value:  $0.0047 \times 10^8$ ).

**Conclusion:** Low dose of intrathecal Dexmedetomidine prolonged the duration of sensory and motor block with the significant sedation level.

**Key Words:** Bupivacaine; Dexmedetomidine; Regional Anaesthesia; Subarachnoid Block

### Introduction

Gynaecological procedures are commonest surgeries done among female patients, which are often done under regional anaesthesia (subarachnoid or epidural block). And hysterectomies are one of them which are often accompanied by visceral and somatic pain.<sup>[1]</sup> Role of adjuvant to local anaesthetics in subarachnoid or epidural block in these surgeries is thus very useful to enhance the quality and duration of block.<sup>[2]</sup> Alpha 2 adrenoreceptor agonist are found to have antinociceptive action for both somatic and visceral pain<sup>[3,4]</sup> Clonidine is already established as adjuvant to Bupivacaine in regional anaesthesia.<sup>[5]</sup> Various studies are going on, to find the effect of Dexmedetomidine as adjuvant. Based on earlier human study it is hypothesized that intrathecal Dexmedetomidine improve duration and quality of subarachnoid block without neurological side effects.<sup>[6]</sup>

This study tested the hypothesis that inclusion of low dose of Dexmedetomidine to intrathecal Bupivacaine in hysterectomies improves the quality of block. Our primary outcomes were onset and duration of sensory

block and motor block. Secondary outcomes were haemodynamic, nausea, vomiting, shivering and sedation.

### Materials and Methods

The protocol of this study was RDBPC (randomized double blind prospective control trial) which was done after taking approval from the hospital ethical committee and explained consent from the patients. This study was done among 60 patients of ASA I-II, Age 35-65 years undergoing either abdominal or vaginal hysterectomies. Excluded from this study were the patients in whom subarachnoid block or study medication was contraindicated or those with the history of psychiatric disorder, cardiovascular, pulmonary, renal, hepatic disease, or patient with history of addiction or drug abuse.

In our study, two groups (N=30) were investigated. Group I (3.5 ml 0.5% hyperbaric Bupivacaine + 0.5 ml of NS 0.9%) and Group II (3.5 ml 0.5% hyperbaric Bupivacaine + 0.5 ml of 5 micrograms Dexmedetomidine) was used.

The anaesthetic solution was prepared according to random number table by means of a computer generated randomization test by another anaesthetist not otherwise involved in this study.

The anaesthetist performing block was blinded to medication. All the observations were carried by single investigator who was blinded to medication. No premedication was given, and patients were preloaded with intravenous 15 ml/kg Ringer lactate solution. Pulse, ECG, Non-invasive BP, Oxygen saturation, monitored for all patients and urethral catheterization done. Subarachnoid block was given to all patients in left lateral position with 25 G spinal needle at L3-L4 level under aseptic condition along with 3.5 ml of Bupivacaine + 0.5 ml of blind solution with different syringe.

Patients were made supine, with mild head low position. Pulse, BP, Oxygen saturation recorded immediately and then in 5 min interval till the end of operation and 10 mints interval postoperative. Onset of sensory block was defined as time interval from intrathecal drug injection to loss of sensation, which was assessed every minute by means of loss of cold sensation (spirit swab) at the level of umbilicus (T10). Onset of motor block was defined as time interval from intrathecal drug injected to loss of toes movements. Onset of motor block was measured every minute by means of asking the patient to move toes up to the Bromage scale of III.

Secondary outcome like nausea, vomiting, shivering, and sedation were noted down by means of visual analogue scale. Level of sedation (0 awake, 1 mild, 2 moderate, 3 deep) and shivering (nil, mild, moderator, severe). Presence of nausea and vomiting noted down (0 means nil to 10 means severe). Hypotension was defined as decrease in systolic blood pressure by more than 30% from baseline. Intravenous drug Ephedrine 6 mg was used to treat hypotension. Bradycardia was defined as pulse below 50/mints and drug Atropine 0.6 mg used to treat it. Drug Tramadol and Ondansetron were given for shivering and nausea vomiting respectively.

Intraoperative 1.5 to 2 liter of crystalline fluid was given according to the duration of surgeries and blood loss. After surgery patients were shifted to recovery room. In post-operative period first dose of analgesic were given on demand, this decided the duration of sensory block (time interval between times of intrathecal drug injected to pain started). Duration of motor block was calculated by noting the time interval between times of intrathecal

drug injected to beginning of toes movements in recovery room. This data was recorded by recovery room nurse.

For statistical analysis, we have used data analysis add in of the Microsoft Excel. Here, we have used f-test to check if the variances of the two columns are same. In case they are same, we have used t-test for two samples assuming equal variances. In case the variances are different, we have used t-test for two samples assuming unequal variances.

## Results

Analysis of patients result revealed no difference in respect to age, BMI, ASA status, duration of surgeries, and type of hysterectomies as shown in table 1. The results regarding the sensory and motor block are summarized in table 2. There was no difference found in onset of sensory block at T10 level. Onset of motor block till Bromage scale III, was found significantly early in group II. The duration of sensory block which measure in the form of rescue analgesic was significantly long with the addition of low dose of Dexmedetomidine. The duration of motor block also gets prolonged in Group II.

**Table-1: Patients' characteristics**

Characteristics	Group I (n=30)	Group II (n=30)
Mean age	42.9 years	46.5 years
BMI	29.1 ± 6.1	31.3 ± 6.2
ASA I, II	30	29, 1
Duration of surgery in mints	62 ± 26.8	59 ± 25.7
Vaginal hysterectomies	15	17
Abdominal hysterectomies	15	13

**Table-2: Primary outcomes**

Outcomes	Group 1 (n=30)	Group II (n=30)	P value
Mean time to reach T10 sensory block level in minutes	4.1	4.2666	0.3579
Mean time to reach motor block till Bromage III, in minutes	6.8666	5.3333	0.006
Mean time of rescue analgesic in minutes	186	286	0.0018×10 <sup>-8</sup>
Mean regression time to Bromage II, in minutes	208.03	299.33	0.0018×10 <sup>-8</sup>

All data expressed in mean; P value < 0.05 is significant

**Table-3: Secondary outcomes**

Outcomes	Group I (n=30)	Group II (n=30)	P values
Sedation	4	22	0.0047×10 <sup>8</sup>
Hypotension	0	4	> 0.05
Bradycardia	0	0	> 0.05
Nausea	4	4	> 0.05
Vomiting	0	1	> 0.05
Shivering	8	5	> 0.05
Others	0	0	> 0.05

VAS: visual analogue scale; P value < 0.05 is significant

In this study, group of patients who received low dose of Dexmedetomidine most of them were found calm, quiet

and comfortable. Out of 30 patients of Group II, 22 patients found sedated, (out of which 21 patients were mildly sedated and 1 patient was moderately sedated). In Group I only 4 patients found sedated (all were mildly sedated) thus we found significant sedation in Group II. There were no other significant complication found in sixty patients like nausea, vomiting, shivering, respiratory depression, bradycardia and hypotension.

## Discussion

Now a day's Regional anaesthesia is preferred over general anaesthesia in lower abdominal and lower limb surgeries due to some advantages like simplicity, maintains airway, less chances of aspiration, benefits in some medical disease and so on. Set back of subarachnoid block using plain local anaesthetics is its limited duration of action. To improve duration of these, adjuvant like Clonidine, Fentanyl, Midazolam and others have been studied.<sup>[7-9]</sup>

Dexmedetomidine produces analgesic effects by an action on  $\alpha_2$  adrenoreceptors within the locus cerulus and the spinal cord. Alpha 2 adrenoreceptors agonist acts by binding to pre-synaptic C-fibers and post-synaptic dorsal horn neurons. The analgesic action of intrathecal  $\alpha_2$  adrenoreceptors agonist is by depressing the release of C -fiber transmitters which explain the prolongation of the sensory block and by hyperpolarisation of post-synaptic dorsal horn neurons which explain the prolongation of the motor block. While local anesthetics act by blocking sodium channels. Prolongation of sensory block may be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetics and the  $\alpha_2$  adrenoreceptors agonist as studied by Salgado et al.<sup>[10]</sup>

Various animal studies have been conducted in rats, rabbits, dogs and sheep using intrathecal Dexmedetomidine without any neurological deficits.<sup>[11-13]</sup> Epidural Dexmedetomidine is being safely used as an adjuvant to Bupivacaine in human being without neurological deficits.<sup>[14]</sup>

In this study our aim was to evaluate the effect of low dose 5  $\mu$ g of intrathecal Dexmedetomidine as an adjuvant to Bupivacaine in hysterectomies. Al-Ghanem et al use 5  $\mu$ g of intrathecal dexmedetomidine in gynaecological procedure have reported the use of Dexmedetomidine to be associated with prolonged duration of sensory and motor block.<sup>[15]</sup> In our study we got early onset of motor

block and long duration of sensory and motor block with significant sedation and haemodynamic stability. Ashraf, and colleagues also have shown a significant longer time to first analgesic request.<sup>[16]</sup> A study done by Kanazi on human being using low dose (3  $\mu$ g) of dexmedetomidine intrathecal with Bupivacaine shown to produce a shorter onset of motor block and prolongation of sensory and motor block with haemodynamic stability and lack of sedation.<sup>[6]</sup>

Alpha2-A agonists act on presynaptic activation of  $\alpha_2$  A receptor in the locus cerulus and inhibit the release of nor-epinephrine, result in sedation and hypnotic effect.<sup>[17]</sup> Intravenous Dexmedetomidine is used as sedative and hypnotic in ICU.<sup>[18]</sup> Dexmedetomidine induce sedation qualitatively resembles normal sleep. The participation of non-rapid eye movement sleep pathways seems to explain why patients who appear to be deeply asleep from Dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep. This type of sedation is branded cooperative or arousable.<sup>[19]</sup> In our study 22 patients out of 30 patients in Dexmedetomidine group were found sedated which were cooperative and arousable. Intrathecal DXM produces this sedation probably because of cephaloid spread or systemic absorption of medicine. Though study done by Rajni Gupta et al using similar dose of Dexmedetomidine intrathecal did not shows significant sedation, hence this need further evaluation.<sup>[20]</sup>

The most important side effect reported about the use of intrathecal  $\alpha_2$  adrenoreceptors agonist is bradycardia and hypotension. In our study these side effect were not significant. No patients of any group had bradycardia and 4 patients out of 30 patients of Group II had hypotension which responds well to intravenous ephedrine and intravenous fluid. Hemodynamic stability might be because of we use small dose of intrathecal DXM which was confirm by Kanazi, AL-Gahem and alka shah in their studies.<sup>[6,15,21]</sup>

Dexmedetomidine reduces the vasoconstriction threshold and the shivering threshold and is associated with lower incidence of shivering.<sup>[22]</sup> Study done by Usta et al and Karaman and colleague showed that intravenous Dexmedetomidine decrease the incidence of shivering.<sup>[23]</sup> Effect of intrathecal Dexmedetomidine yet not found reducing shivering in any study. In our study though incidence of shivering of were found less in Dexmedetomidine group, (5 as compare to 8) but

statistically it was not significant.

Hala E A Eid MD, Mohamad A shafie MD, Hend Youssef MD, did a study, they use 10 µg and 15 µg of intrathecal dexmedetomidine and found that, by increasing the dose of Dexmedetomidine, the quality of blocks and sedation gets improved but hemodynamic were maintained.<sup>[24]</sup> Thus 5 µg of intrathecal DXM is low and safe dose to increase the duration of block, and there is a scope for further increasing the dose and duration of block.

Dexmedetomidine as intrathecal adjuvant is not advisable in day care surgeries or short and ambulatory surgeries as it increase the duration of motor block.

We chose hysterectomies as these patients suffer perioperative somatic and visceral pain and need good perioperative analgesia and alpha2-A agonist are found to have antinociceptive action for both somatic and visceral pain.<sup>[3]</sup> All the patients were subjected to similar kind of pain, which made our inference more specific and correct, though subjective variation is always there. Because of fear and pain Post operatively patients do not move their legs. Hence duration of motor blocks result might be not up to the mark.

## Conclusion

To improve the quality and duration of subarachnoid block various adjutants are under use. Dexmedetomidine, which is more potent than Clonidine, increases quality of subarachnoid block by increasing duration of sensory and motor block with good level of sedation, maintain haemodynamic and minimal side effects. We concluded that, we can safely add low dose (5µg) of intrathecal Dexmedetomidine to Bupivacaine to increase the duration of block in hysterectomies or other procedures that need quite long time and associated with somatic and visceral pain.

## References

- Alahuhta S, Kangas-Saarela T, Hollmén AI, Edström HH. Visceral pain during caesarean section under spinal and epidural anesthesia with Bupivacaine. *Acta Anaesthesiol Scand* 1990;34:95-8.
- Shetty PS, Picard J. Adjuvant agents in regional anesthesia. *Anesth Intensive Care Med* 2006;7:407-10.
- Harada Y, Nishioka K, Kitahata LM, Kishikawa K, Collins JG. Visceral antinociceptive effects of spinal Clonidine combined with morphine, encephalin, or U50, 488H. *Anesthesiology* 1995;83:344-52.
- Kalso E, Poyhia R, Rosenberg P. Spinal antinociception by dexmedetomidine, a highly selective α2-adrenergic agonist. *Pharmacol Toxicol* 1991;68:140-3.
- Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: Systematic review of randomized trials. *Reg Anesth Pain Med* 2008;33:159-67.
- Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand* 2006;50:222-7.
- Boussofara M, Carlès M, Raucoules-Aimé M, Sellam MR, Horn JL. Effects of intrathecal midazolam on postoperative analgesia when added to a bupivacaine-clonidine mixture. *Reg Anesth Pain Med* 2006;31:501-5.
- Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for Cesarean delivery. *Anesthesiology* 1989;71:535-40.
- Prakash SI, Joshi N, Gogia AR, Prakash S, Singh R. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. *Reg Anesth Pain Med* 2006;31:221-6.
- Salgado PF, Sabbag AT, Silva PC, Brienze SL, Dalto HP, Modolo NS, et al. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. *Rev Assoc Med Bras* 2008;54:110-5.
- Eisenach JC, Shafer SL, Bucklin BA, Jackson C, Kallio A. Pharmacokinetics and pharmacodynamics of intraspinal dexmedetomidine in sheep. *Anesthesiology* 1994;80:1349-59.
- Lo WC, Harris J, Clark RW. Endogenous opioids support the spinal inhibitory action of an alpha 2- adrenoceptor agonist in the decerebratespinalised rabbit. *Neurosci Lett* 2003;340:95-8.
- Talke P, Xu M, Paloheimo M, Kalso E. Effect of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine on EMG in rats. *Acta Anaesthesiol Scand* 2003;47:347-54.
- Konakci S, Adanir T, Yilmaz G, Rezanko T. The efficacy and neurotoxicity of dexmedetomidine administered via the epidural route. *Eur J Anaesthesiol* 2008;25:403-9.
- Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, et al. Effect of Adding Dexmedetomidine versus Fentanyl to Intrathecal Bupivacaine on Spinal Block Characteristics in Gynecological Procedures: A Double Blind Controlled Study. *Am J Appl Sci* 2009;6:882-7.
- Mohamed AA, Fares KM, Mohamed SA. Efficacy of intrathecally administered Dexmedetomidine Versus Dexmedetomidine with Fentanyl in patients undergoing major abdominal cancer surgery. *Pain Physical* 2012;15:339-48.
- Jones MEP, Maze M. Can we characterize the central nervous system action of alpha 2 adrenoceptors agonist ? *British Journal of Anesthesia* 2001;86:1-3.
- Shehabi Y, Botha JA, Ernest D, Freebairn RC, Reade M, Roberis BL, et al. clinical application, the use of dexmedetomidine in intensive care sedation. *Crit care shock* 2010;13:40-50.
- Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. *J Clin Anesth* 1993;5:194-203.
- Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. *Indian J Anaesth* 2011;55:347-51.
- Eisenach JC, De Kock M, Klimscha W. α2-Adrenergic Agonists for Regional Anesthesia: A Clinical Review of Clonidine (1984 - 1995). *Anesthesiology* 1996;85:655-74.
- Gertle R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine; a novel sedative-analgesic agent. *Proc (Bayl Univ Med Cent)* 2001;14:13-21.
- Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richard C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1997;87:835-41.
- Hala EA, Eid MD, Mohamed A, Shafie MD, Hend Youssef MD. Dose-related prolongation of hyperbaric bupivacaine spinal anesthesia by dexmedetomidine. *Ain Shams J Anesthesiol* 2011;4:83-95.
- Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, et al. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. *Saudi Med J*

- 2009;30:365-70.
26. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. Comparative study of intrathecal Dexmedetomidine and Fentanyl as adjuvants to Bupivacaine. *J anaesthesiol clin pharmacol* 2011;27:339-43.
27. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richard C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1997;87:835-41.
28. Fukushima K, Nishimi Y, Mori K, Takeda J. Effect of epidurally administered dexmedetomidine on sympathetic activity and postoperative pain in man. *AnesthAnalg* 1996;82:S121.

**Cite this article as:** Bansal SA, Bansal VA. A randomized controlled double-blinded prospective study of the efficacy of low dose of Dexmedetomidine as an adjuvant to intrathecal Bupivacaine in hysterectomies. *Int J Med Sci Public Health* 2014;3:876-880.

**Source of Support:** Nil

**Conflict of interest:** None declared

IJMSPH