Original Research Article

Intrathecal dexmedetomedine and magnesium sulphate as an adjuvants to hyperbaric bupivacaine in pregnancy induced hypertensive patients: A clinical comparative study

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Abstract

Background and Aims: Providing a safe anaesthesia and analgesia with a stable hemodynamic and with no neonatal adverse effects to a preeclamptic caesarean patients is a challenging task. Various adjuvants have been tried with intrathecal bupivacaine in the past to achieve this goal. This study was designed to evaluate and compare the analgesic efficacy of dexmedetomedine and magnesium sulphate when used as an adjuvant to intrathecal 0.5% bupivacaine in mild preeclamptic patient posted for caesarean. **Methods:** Sixty patients of mild preeclampsia posted for caesarean section under spinal anaesthesia were randomly allocated into two groups. Group D received 2ml 0.5% bupivacaine with 10 micro grams of dexmedetomedine and group M received 2ml 0.5% bupivacaine with 50 mg of magnesium sulphate. The primary outcome was duration of postoperative analgesia and secondary outcomes were onset and duration of sensory and motor block, hemodynamic changes, sedation and neonatal APGAR and ABG values. Data were analysed with the Kolmogorov-Smirnov test, independent t-test and chi-square test. **Results:** The time to reach peak sensory level was shorter in group D (4±0.4 min) than group M (8.0±0.9min) with a $p<0.001$. In Group D the duration of motor block was longer (200±6.1 min vs 180±8 min) with the early onset of motor block (6.3±0.7 min vs 6.9±0.9) compared with group M. The onset of postoperative pain was significantly earlier in group M (160±27 min vs 243±35 min) with a p value < 0.001 and more patients in group M (26/30 vs 9/30) needed supplementary analgesics than group D. No clinically significant difference was observed in the rate of occurrence of hypotension and bradycardia between the two groups. No significant difference was observed between the two groups regarding the APGAR score and maternal side effects like sedation.

Key Words: Dexmedetomedine, Intrathecal, Magnesium sulphate, Pregnancy Induced Hypertension.

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INTRODUCTION

A stable hemodynamic with pain free postoperative period is very much essential for a preeclamptic caesarean mother, to have an uneventful postnatal period and to start developing bondage with the neonate. Intrathecal bupivacaine with various adjuvants have been tried in the past to achieve this goal.[1] Though opioids like low dose morphine and fentanyl have been tried to in the past to prolong the analgesia but at a cost of high incidence of nausea and vomiting.[1] During pregnancy an alpha 2 agonist Dexmedetomidine has been tried by various routes with favourable maternal and neonatal

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outcome.[2-9] Dexmedetomidine has 8 times greater affinity to the alpha 2 receptor than the clonidine[2] and it has both sedative and analgesic properties when used in regional techniques.[10] An NMDA agonist Magnesium sulphate has also been used intrathecally with favourable outcomes. It prevents the central sensitisation of pain by non-competitive antagonism of NMDA receptors and by regulating voltage dependent calcium influx.[11] A comparative study between intrathecal Dexmedetomidine and magnesium sulphate with 0.5% heavy bupivacaine has been done to assess the analgesic properties and safety profile in preeclamptic caesarean patients.

MATERIALS AND METHODS

After obtaining ethical committee clearance from Chamarajangar Institute of Medical Sciences, a total of sixty patients diagnosed with mild preeclampsia undergoing elective caesarean section aged between 18 to 35 years belonging to ASA I and II were randomly allocated into two groups: A Dexmedetomidine group (group D, n-30) –patients received 2ml 0.5% heavy bupivacaine (NEON laboratories, Mumbai, India) with 0.1 ml of 10 µg Dexmedetomidine (THEMIS MEDICARE LIMITED, Uttarakhand, India) intrathecally. A magnesium sulphate group (group M, n-30)- patients received 2ml 0.5% bupivacaine with 0.1 ml of 50mg of magnesium sulphate (50%) (Harson Laboratories, India). Exclusion criteria were patient's refusal for spinal anaesthesia, Eclampsia, seizure disorder, Heart disease, arrhythmias, dehydrated conditions, Foetal distress, coagulation disorder, allergy to local anaesthetic drugs. Randomisation was done by using a computer-derived random-number sequence and sealed opaque envelopes, and all investigators were kept unaware of the envelope details throughout the whole study period. After a detailed preanaesthetic check-up, informed written consent was obtained from the parturient. After arrival to the operation theatre, standard anaesthesia monitors were attached to the patient including pulseoxymeter, non-invasive arterial blood pressure and SpO2 and ECG and baseline readings were recorded. An intravenous cannula was placed. The patients were preloaded with normal saline 0.9% (15 ml/kg) infused over 20 min. Spinal anaesthesia was performed in lateral position at the L3-L4 level using a 25 G Quincke spinal needle under proper aseptic conditions. Onset of sensory block was assessed every 1 minute by pinprick in the midclavicular line until a stable level is achieved. The duration of sensory block was the time from spinal injection to regression of sensory block to T12. The duration of spinal anaesthesia was the period from the spinal injection to the first rescue analgesic administration in the postoperative period. Motor block was assessed using a modified bromage score (0= no motor block, 1=inability to flex hip, 2=inability to flex hip and knee, 3=inability to flex hip, knee and ankle), with motor recovery assumed when the score was zero. Haemodynamic parameters like heart rate, mean arterial pressure and oxygen saturation were recorded every 1 minute interval for the first 10 minute, and then every 3 minutes till the end of surgery and then every 15 minutes in the post anaesthesia care unit (PACU) until the patient was discharged. Hypotension of fall in systolic pressure>20% below baseline was treated with fluids and 6 mg boluses of mephenteramine. Bradycardia of heart rate less than 60 was treated with i.v atropine sulphate (0.6 mg). The total doses of atropine and mephenteramine required in both the groups were noted. Side effects like sedation, was noted in both the groups every 15 minutes during surgery and then at 2, 4, 8, 12 and 24 h postoperatively. Sedation was measured using the Ramsay sedation score. 1=cooperative, oriented, tranquil, 2=responds to commands only, 3=brisk response to light glabellar tap or loud noise, 4=sluggish response to light glabellar tap or loud noise, 5=no response. Post-operative analgesia was assessed by 10 point verbal rating scale in which 0 represented no pain and 10 represented worst possible pain. Intramuscular diclofenac was given for pain greater than 4. The time of the first rescue analgesia and number of patients who required were recorded. Neonatal parameters like Apgar score, PH, PCO2, PO2 and need for resuscitation were recorded. Patients were observed for next 24 hrs regarding any complications such as hypotension, bradycardia, respiratory depression, nausea and vomiting, and managed them accordingly.

Study Outcome: The primary outcome of the study was the duration of the postoperative analgesia(the time to the first rescue analgesia) and the secondary outcomes were the onset and duration of sensory and motor blockade, possible dexmedetomedine side effects(hypotension, excessive sedation, bradycardia) and side effects in the new born(APGAR scores and umbilical cord blood gas analysis). All statistical analyses were performed using Epi-Info 7.2 software for windows. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Parametric data were compared using independent t-test. All the categorical data were compared by using chi-square test. A sample size of 30 patients per group was needed to detect an intergroup difference of at least 20% (α= 0.01, two-sided, power = 90%) with two sample t-test. A value of $P < 0.05$ was considered statistically significant. The results are expressed as mean (SD).

RESULTS

Table 1:

	Group M	Group D	P value
Age (years)	26 ± 4	27 ± 4	0.3369
Height (cms)	154 ±5	156 ±3.5	0.0779
Weight (kg)	62.5 ±2.3	63.2 ±2.9	0.3046
Duration of surgery (min)	66 ±11	65.2 ±9	0.7590
Gestational age (wks)	36 ±1	36.3 ±0.8	0.2046

Data are presented as mean ± SD, P<0.05 is considered as statistically significant.

Table 2: Characteristics of spinal anaesthesia

	Group M	Group D	P value
Highest sensory level T4 T6	 10/30 20/30	 8/30 22/30	NS
Time to maximum sensory level (min)	8.0±0.9	4±0.4	< 0.0001
Time to T10(min)	6.5±0.4	3.1±0.3	< 0.0001
Time to regress to S1(min) (duration)	210±9	280±10	< 0.0001
Time for complete motor block (mod bromage 3)	6.9±0.9	6.3±0.7	0.0055
Time for complete motor recovery (mod brom 0)	180±8	200±6.1	< 0.0001

Data are presented as mean ± SD, P<0.05 is considered as statistically significant.

Table 3: Changes in haemodynamic parameters

	Group M	Group D	P value
Baseline SPO2	99 ±0.9	99± 0.6	0.999
Lowest SPO2	99± 0.3	99± 0.1	0.999
Baseline HR	80± 4	78± 3.5	0.0438
Lowest HR	63± 3.2	62± 4.2	0.240
Baseline MAP	94.1± 5	96± 4	0.1095
Lowest MAP	80.1 ±3.1	77.8± 4.2	1

Data are presented as Mean ± SD; HR heartrate; MAP, mean arterial pressure; p, <0.05 statistically significant.

Table 4: Intraoperative and postoperative Ramsay sedation score

	Group M	Group D	P value
Intra op. Sedation	1(1-1.5)#	3(2-3)	<0.001
Post op. sedation at 6 hrs	1(1-2)	3(2-3)	<0.001
Post op. sedation at 12 hrs	1(1-2)	1(1-2)	0.65

Data are presented as Median (IQR); IQR, interquartile range; # p<0.05 statistical significant.

Table 5: Neonatal parameters

	Group M	Group D	P value
weight	2.8±0.4	2. 9±0.6	0.4506
APGAR @5 min @10 min	8 9	8 9	NS NS
PH	7.30±0.1	7.31±0.1	0.7
PO2	36.8±1.5	36.6±1.0	0.5458
PCO2	38±1.4	38.6±1.5	0.1147
Need for resuscitation	Nil	Nil	

Data are represented as mean ± SD, p<0.05 statistically significant.

Table 6: Characteristics of analgesia

	Group M	Group D	P value
% of patients with effective analgesia 3 hrs after spinal anaesthesia (VAS<3)	26/30#	9/30	< 0.0001
Time for first request of analgesia (min)	160±27#	243±35	< 0.0001

Data are represented as mean ± SD or the number of patients; #p<0.05 statistically significant. The time to reach peak sensory level was significantly shorter in group D. The duration of motor block was shorter in

group M with no clinically significant difference between two groups in onset of motor block. Onset of postop pain was significantly earlier in group M and more patients in group M needed supplementary analgesics than group D. No significant difference was observed between two groups regarding maternal hemodynamic and neonatal APGAR and ABG values. Though the Group D patients were more sedated than Group M, it lasted only for 6 hrs postoperatively and after that both the groups were similar with respect to sedation.

DISCUSSION

Dexmedetomedine is a highly selective alpha 2 agonist with an affinity 8 to 10 times higher than that of clonidine.[2] Alpha 2 agonist have both analgesic and sedative effects by binding to alpha 2 receptors in the locus coeruleus which diminishes the release of norepinephrine and inhibits sympathetic activity.[12-14] The alpha 2 agonist acts by binding to presynaptic C fibres and post synaptic dorsal horn neurons, thus depressing the release of C fibre transmitters and hyperpolarising dorsal horn post synaptic neurons. Therefore this may cause additive synergistic effect to the mechanism of action of local anaesthetics.[12] Previously as it has been shown in many studies[15-18] intrathecal dexmedetomedine prolongs the duration of sensory and motor block of spinal anaesthesia. In the current study also dexmedetomedine has prolonged the sensory block and to a lesser extent prolonged the motor block of bupivacaine. The dose required to inhibit A alpha fibres is 4 times higher than the dose required to inhibit C fibres hence at low dose its effect on motor block is less where as it prolongs analgesia and sensory block.[19] This may explain the lesser effect on motor block compared with sensory block observed in our study. Dexmedetomedine is a selective alpha 2 agonist with dose dependent analgesic effect and sedative effect. In our study low dose dexmedetomedine has resulted in significant reduction in VAS score postoperatively with consequent delay in the time to first request of analgesia postoperatively. In a study done by *Belleville JP et al* it was shown that patients remain cooperative and easily arousable when sedated with low dose dexmedetomedine.[20] In our study patients with low dose intrathecal dexmedetomedine had mild sedation intraoperatively and 6hrs postoperatively which provided better conditions for the surgeons and the patients. Dexmedetoedine when administered intrathecally in high doses can cause hypotension and bradycardia[21] whereas when used at lower doses as we have used at 10 micrograms with proper preloading incidence of hemodynamic disturbances and other side effects are less. Hypotension that was observed was treated with ephedrine and left uterine displacement. As it is shown in many studies use of dexmedetomedine has not resulted in any neurological disturbances within 2 weeks after surgery.[13,17,19,21] Though bradycardia was observed in 4 out of 30 patients in dexmedetomedine group, it very well responded to atropine. Similarly bradycardia was observed in various studies[13,17,19,21] which could be reversed by atropine with no side effects. The bradycardia inducing effect of dexmedetomedine in these studies may be explained by the decreased sympathetic outflow and the decreased catecholamine effects.[22] Being a highly lipophilic drug Dexmedetomedine has a high placental retention (0.77 maternal /foetalindex). As a result it is retained in the placental tissue and does not cross the placental barrier or crosses in a negligible manner.[4-5] In our study there was no neonatal effect of dexmedetoedine compared to magnesium sulphate with respect to APGAR score and ABG values. Magnesium sulphate NMDA antagonist acts as an effective spinal adjuvant. Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which binds to the NMDA receptors. Post activation of these receptors calcium enters into the cell and initiates a series of central sensitisation such as windup and long term potentiation[23] which is important in determining the duration of acute pain.[24] Magnesium blocks calcium influx and noncompetitively antagonises NMDA receptor channels.[25] Magnesium prevents the induction of central sensitisation and prolong the sensory and analgesia of anaesthetics. The onset and resolution of sensory and motor block was prolonged in our study. Similar finding was seen with *Katiyar S et al*. Magnesium induced delayed spinal anaesthesia could be explained by alteration of the pharmacokinetic of intrathecal bupivacaine. It might be because of differences in baricity and pH between the solution containing magnesium sulphate and cerebrospinal fluid which causes cytochrome P450 induced hydrolysis of intrathecal bupivacaine by magnesium.[26] The delay in onset was more pronounced with higher doses compared to lower (100mg, 75 mg vs 50 mg).[27] It provides the rationale for choosing the dose of magnesium sulphate for our study. Similar to our study *Arcioniet al* also observed that intrathecal magnesium sulphate prolonged motor block.[28] Our study did not find an increase in sedation or respiratory depression following intrathecal magnesium. Although these side effects are more often reported in eclamptic parturients treated with iv magnesium.[29] Though the hypotension observed in eclampsia with i.v. magnesium is due to systemic vasodilatory effect, it was not seen with intrathecal magnesium.[30] This is due to local action of magnesium sulphate on spinal nociceptive pathways and the absence of systemic effects when given intrathecally. Although the prolonged duration of sensory blockade with dexmedetomedine can improve

postoperative pain management the delayed recovery of motor function may have its disadvantages and may be inappropriate in day care settings. Although various studies established analgesic efficacy of both intrathecal dexmedetomedine and magnesium sulphate none of them compared simultaneously. Hence we had conducted this comparative study to evaluate the beneficial effects of dexmedetomedine and magnesium sulphate in PIH parturients and also to look for any adverse effects on the mother and the neonate.

CONCLUSION

According to our study we could conclude that 10 micrograms of dexmedetoedine intrathecally is an attractive alternative as an adjuvant to intrathecal bupivacaine for mild preeclamptic caesarean patient, with excellent postoperative analgesia and with minimal maternal side effects and without any significant changes in neonatal blood gas parameters in comparison to magnesium sulphate. Further studies are required to determine the highest and the safe dose of dexmedetomedine and magnesium sulphate which could be used in parturients with mild preeclampsia which might further prolong postoperative analgesia without any unwanted maternal and neonatal side effects.

REFERENCES

1. Slappendel R, Weber EW, Benraad B, Van Limbeek J, Dirksen R. Itching after intrathecal morphine. Incidence and treatment. Eur J Anaesthesiol 2000; 17:616-621.
2. Hanoura SE, Hassanin R, Singh R. Intraoperative conditions and equality of post-operative analgesia after adding dexmedetomedine to epidural bupivacaine and fentanyl in elective caesarean section using combined spinal epidural anaesthesia. Anesth Essays Research 2013; 7:168-172.
3. Organ SF, Job OG, Enyindah CE. Comparative effects of single shot intrathecal bupivacaine with dexmedetomedine and bupivacaine with fentanyl on labour outcome. ISRN Anesthesiol 2012; 2012:816984.
4. Karaman S, Evren V, Cankayali I. The effects of dexmedetomedine on spontaneous contractions of isolated gravid rat myometrium. Adv Ther 2006; 23:238-243.
5. Tariq M,Cermy v, Elfaki I, Khan HA. Effects of sub chronic versus acute inutero exposure to dexmedetomedine on foetal development in rats. Basic Clin Pharmacol Toxicol 2008; 103:180-185.
6. Souza KM, Anzoategui LC, Pedroso WC, Geperli WA. Dexmedetomedine in general anesthesia for surgical treatment of cerebral aneurysm in pregnant patient with specific hypertensive disease of pregnancy: case report. Rev Bras Anesthesiol 2005; 55:212-216.
7. Abu-Halaweh SA, Al oweidi AK, Abu-Malooh H, Zabalwi M, Alkazaleh F, Abu Ali H, Ramsay MA. Intravenous dexmedetomedine infusion for labour analgesia in patient with preeclampsia. Eur J Anaesthesiol 2009; 26:86-87.
8. Palanisamy A, Klickovich RJ, Ramsay M, Ouayang DW, Tsen LC. Intravenous dexmedetomedine as an adjunct for labour analgesia and caesarean delivery anesthesia in a parturient with a tethered cord. Int J Obstet Anesth 2009; 18:258-261.
9. El-Tahan MR, Mowafi HA, Al sheikh IH, Khidr AM, Al-Juhaiman RA. Efficacy of dexmedetomedine in supressing cardiovascular and hormonal responses to general anaesthesia for caesarean delivery: a dose response study. Int J Obstet Anesth 2012; 21:222-229.
10. Hall JE, Uhrich TD, Barney JA, Arrain SR, Ebert TJ. Sedative, Anaesthetic and analgesic properties of small dose of dexmedetomedine infusions. Anesth Analg 2000; 90:699-705.
11. Morrison AP, Hunter JM, Halpern SH, Banerjee A. Effect of intrathecal magnesium in the presence or absence of local anaesthetic with and without lipophilic opioids: A systematic review and meta-analysis. Br J Anaesth 2013; 110:702-12.
12. Eisenach JC, De Kock M, Klimscha W. alpha (2) – adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995).Anaesthesiology 1996; 85:655-674.
13. Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, Al-Ghanem BM. Intravenous dexmedetomedine prolongs bupivacaine spinal analgesia. Middle East J Anaesthesiol 2009; 20:225-231.
14. Kaya FN, Yavascaoglu B, Turker G, Yildirin A, Gurbet A, Mogol EB, Ozcan B, Intravenous dexmedetomedine but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth 2010; 57:39-45.
15. Solanki SL, Bharati YK, Jain A, Kumar P, Nikhar SA. The analgesic effect of intrathecal dexmedetomedine or clonidine, with bupivacaine in trauma patients undergoing lower limb surgeries: A randomised double blind study. Anaesth Intensive Care 2013; 41:51-56.
16. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, et al. Effect of Dexmedetomedine added to spinal bupivacaine for urologic procedures. Saudi Med J 2009; 30:365-370.
17. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, et al: Effect of low dose dexmedetomedine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006; 50:222-227.
18. Gupta R, Bogra J, Verma R, Kohli M, Kushwaha JK, Kumar S. Dexmedetomedine as an intrathecal adjuvant for postoperative analgesia. Indian J Anaesth 2011; 55:347-351.
19. Elcicek K, Tekin M, Kati l. The effects of intravenous dexmedetomedine on spinal hyperbaric ropivacaine anesthesia. J Anaesth 2010; 24:544-548.
20. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomedine in humans. Sedation, ventilation, and metabolic rate. Anesthesiology 1992; 77: 1125-1133.
21. Hong JY, Ki WO, Yoon Y, Choi Y, Kim SH, Kil HK. Effects of intravenous dexmedetomedine on low dose bupivacaine spinal anesthesia in elderly patients. Acta Anaesthesiol Scanda 2012; 56:382-387.

22. Eisenach JC, De Kock M, Kimscha W: Alpha 2 adrenergic agonists for regional anaesthesia. A clinical review of clonidine (1984-1995). Anaesthesiology 1996; 85:655-674.
23. Pockett S. Spinal cord synaptic plasticity and chronic pain. Anesth and Analg 1995; 80:173-9.
24. Woolf CJ, Thompson SW. The induction and maintenance of central sensitisation is dependent on N-methyl-O-aspartic acid receptor activation; Implications for the treatment of post injury hypersensitivity states. Pain 1991; 44:293-9.
25. Fawcett WJ, Haxby EJ, Male DA. Magnesium: Physiology and Pharmacology. Br J Anaesth 1999; 83:302-20.
26. Katiyar S, Dwivedi C, Tipu S, Jain RK. Comparison of different doses of magnesium sulphate and fentanyl as adjuvants to bupivacaine for infraumbilical surgeries under subarachnoid block. Indian J Anaesth 2015; 59:471-5.
27. Jabalameli M Pakzadmoghadam SH. Adding different doses ofintrathecal magnesium sulphate for spinal anaesthesia in the caesarean section: A prospective double blind randomised trial. Adv Biomed Res 2012; 1; 7.
28. Arcioni R, Palmisoni S, Tigano S, et al. combined intrathecal and epidural magnesium sulphate supplementation of spinal anaesthesia to reduce post-operative analgesic requirements: a prospective, randomised, double blind, controlled trial in patients' undergoing orthopaedic surgery. Acta Anesthesiol Scand 2007; 51:482-9.
29. Witlin AG, Sibai BM. Magnesium sulphate therapy in preeclampsia and eclampsia. Obstet Gynaecol 1998; 92:883-9.
30. Duley L, Watkins K. Magnesium sulphate for treatment of preeclampsia: a trial to evaluate the effects on woman and their babies. Contempt Rev Obstet Gynaecol 1998:10:267-74.

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