Indian Journal of Clinical Anaesthesia 2019;6(4):481–487

Content available at: iponlinejournal.com

Indian Journal of Clinical Anaesthesia

Journal homepage: www.innovativepublication.com

Original Research Article

Comparison of intrathecal Tramadol and Magnesium sulfate as an adjuvant to Levobupivacaine in mild Pre-eclamptic parturients undergoing caesarean section- A prospective randomized control study.

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ARTICLE INFO

Article history:
Received 02-05-2019
Accepted 29-08-2019
Available online 20-11-2019

Keywords:
Intrathecal
Levobupivacaine
Magnesium sulfate
Preeclampsia
Tramadol

ABSTRACT

Aims and Objective: Spinal anaesthesia is advantageous as compare to general anaesthesia for cesarean section especially in preeclampsia as it avoids the complications of general anaesthesia. To improve the quality of sensory and motor blockade and prolong the duration of postoperative analgesia, we had used tramadol and magnesium sulfate intrathecally with the primary aim to assess sensory and motor blockade and postoperative analgesia.

Material and Methods: This prospective randomized control study included sixty preeclamptic parturient having more than 36 weeks of pregnancy with controlled hypertension aged 18-40 years with single pregnancy, planned for caesarean section of ASAPS II, III and able to understand VAS score were included. Parturients were randomly assigned to g roup LT (injection Levobupivacaine 0.5%, 1.5ml + injection Tramadol 25 mg,0.5ml) and group LM (injection Levobupivacaine 0.5%, 1.5ml + injection Magnesium sulfate 100 mg,0.5ml) using computer generated random numbers and the assignment was sealed in envelopes for concealment. They were assessed for sensory blockade, motor blockade and postoperative analgesia.

Results: The onset of sensory block was late in group LM [102sec (102-105) sec] in comparison to group LT [69sec (66-72) sec, *P<0.0001]*. The time to attain peak sensory level was late in group LM [2min (1.9-2) min] in comparison to group LT [1.6min (1.5-1.6) min, *P<0.0001]*. The motor block onset was delayed in group LM [93.5sec (92-95) sec] compared to group LT [60sec (58-63) sec, *P<0.0001]*. The duration of post-operative analgesia was extended further for group LM [570min (540-600) min], in comparison to group LT [357min (342-360) min, *P<0.0001]*.

Conclusion: Intrathecal magnesium sulfate can be considered as a desirable adjuvant to Levobupivacaine in mild preeclamptic parturients undergoing cesarean section compared to tramadol.

1. Introduction

Spinal anaesthesia (SA) is most commonly used anaesthesia technique for cesarean section (CS) even in severe preeclampsia, largely because of the recognition of the dangers of difficult or failed intubation, which occurs approximately eight times more frequently in pregnant patients.[1,2] Among the local anaesthetics, levobupivacaine is truly isobaric to cerebrospinal fluid(CSF) of pregnant women and provides sympathetic blockade which is not affected by change in position.[3] But the postoperative analgesia is reported to be of short duration if only local anaesthetics is used for SA. Various studies reported magnesium sulfate is an effective adjuvant to intrathecal local anaesthetics as far as postoperative analgesia is concerned in pregnant as well as nonpregnant patients.[4,5] Tramadol, another adjuvant to intrathecal local anaesthetics, extends the duration of postoperative analgesia but it is devoid of respiratory depression.[6] Hence, we decided to compare a centrally acting analgesic Tramadol and NMDA

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https://doi.org/10.18231/j.ijca.2019.094

receptor antagonist Magnesium sulfate to intrathecal levobupivacaine in mild preeclamptic parturient undergoing CS. Our primary aim was to assess sensory and motor blockade plus postoperative analgesia while secondary aim was to see hemodynamic parameters and complications, if any.

2. Material and Methods

This prospective randomized control study was carried out following approval from the Scientific research committee and Institutional Ethics Committee for Human Research during the period of March to October 2017. Written informed consent of each parturient was obtained. A thorough preanaesthetic assessment was carried out. History was taken regarding present and past complaints, personal history, medication history, history of previous anaesthesia experience, blood transfusions, jaundice etc. General and systemic examination was done. Routine and specific investigations like liver function test, bleeding time, clotting time, prothrombin time, INR and platelet count were carried out. Total sixty preeclamptic parturient aged 18-40 years having more than 36 weeks of pregnancy with controlled hypertension with singleton pregnancy, undergoing elective CS having normal bleeding profile (BT, CT, PT), of ASA physical status II, III and was patient able to give written informed consent and understand VAS score were included. Parturient with signs of HELLP syndrome, fetal distress, patients with contraindications to spinal anaesthesia, significant history of drug or alcohol abuse, morbid obesity (BMI >35 kg/m^2), previous LSCS, diabetic, neurological or musculoskeletal diseases, unable to understand VAS, on magnesium therapy or having placenta previa or abruptio placenta were excluded from the study. They were kept nil by mouth overnight. Intravenous line was secured with a 18g veinflow. All parturients were preloaded using injection ringer lactate @ 10ml/kg over 15 minutes prior to spinal anaesthesia. All were premedicated with injection Glycopyrrolate 0.2 mg, injection Metoclopramide 10mg, injection Ranitidine 50mg intravenously 5 min before induction. Patients were randomly assigned into two groups. For randomization, computer generated random numbers were used. And its concealment was assured by sealing it in envelopes. They were assigned into Group LT (injection Levobupivacaine 0.5%, 1.5ml + injection Tramadol 25 mg,0.5ml) and Group LM (injection Levobupivacaine 0.5%, 1.5ml + injection Magnesium sulfate 100 mg,0.5ml.) Magnesium sulfate was prepared using 5 ml disposable syringe. Two ml of magnesium sulfate diluted with sterile water up to 5 ml, so 1 ml = 200 mg and from that 0.5ml (100mg) was taken. In both the groups the volume of study drug was 2 ml. Inside the operation theatre, multipara monitor was used and base line pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation (SpO_2) were noted down. Parturient was placed in left lateral decubitus position and with all aseptic and antiseptic precautions, 23 G Quincke's spinal needle was inserted in third or fourth lumber intervertebral space in the midline. After confirmation of the needle tip in subarachnoid space, study drug was injected over 10 sec. Parturient was turned to supine position and wedge under right buttock was kept soon after and Oxygen at the rate of 4L/min using non-rebreathing mask was given. They were assessed for sensory blockade, motor blockade and postoperative analgesia. Sensory block was assessed using pin prick method in midclavicular line bilaterally at 30 sec then every minute till 5 min and then at 7,10 min and looked for onset of sensory block (time from drug injection to loss of pin prick sensation at T_{12} level in sec), maximum level achieved, time to achieve maximum level (time elapsed from the end of injection to attain maximum level of sensory block in minute), time to two segment regression of block (checked half hourly after max height achieved in min) and duration of sensory block i.e. time interval from loss of pin prick at T_{12} dermatome to reappearance of pin prick at T_{12} dermatome in min. Motor block was assessed at 30 sec then every minute till 5 min and then at 7,10 min using modified Bromage grade (Appendix1).[1]

2.1. Appendix 1: modified bromage grade

Grade 0=Patient is able to move the hip, knee and ankle.

Grade 1= Patient is unable to move hip, but is able to move knee and ankle.

Grade 2=Patient is unable to move hip and knee but is able to move ankle.

Grade 3=Patient unable to move hip, knee and ankle.

We looked for onset (time to achieve bromage grade 1 in minute), complete motor block (time to attain bromage grade 3 in minute), duration of motor block (time from onset to when bromage grade become 0 in minute). A visual analogue scale (VAS) score was used to assess postoperative analgesia every hour up to 4 h followed by every 2 h for 24 h. and was evaluated using a VAS as mild (0-3), moderate (4-7) and severe (8-10). Injection Diclofenac sodium 75 mg intramuscularly was given when VAS $\geq$ 4 or on patient demand as a rescue analgesia. We observed duration of absolute analgesia (min), postoperative analgesia and the number of rescue analgesia required for 24 h postoperatively. Absolute analgesia was defined as the duration from intrathecal injection of drug to first sensation of any pain at the site of surgery in minutes and duration of postoperative analgesia as duration from completion of surgery to first rescue analgesic in minutes. Patients were also observed for vital parameters like pulse rate, SBP, DBP and SpO_2 at various interval after giving SA upto the end of surgery. Duration of surgery and blood loss were noted. Neonatal Outcome was assessed by noting APGAR score at 1,5,10 min, requirement of tracheal intubation as yes/no

and mask ventilation as yes/no. The parturients were also observed for perioperative complications like bradycardia (it was defined as pulse rate <60/minute or fall in pulse rate of 20% of baseline, injection Atropine 0.6 mg intravenous was given), hypotension (it was defined as 30% fall in SBP from baseline, treated with intravenous fluids, oxygen and intravenous ephedrine 5mg.), respiratory depression, nausea and vomiting and neurological complications.

MedCalc software was used for the calculation of sample size by taking mean and standard deviation value for the parameter "maximum sensory level achieved" derived from reference.[3] The difference of means 0.6 and SD 0.89 and 0.76, taking α error as 5%, β as error 20%, confidence interval 95%, minimum sample size came out to be 30 in each group. A master chart was prepared to arrange the observed parameters of each and every case in Microsoft Excel 2016. MedCalc for Windows, version 12.7.5.0 (MedCalc Software, Ostend, Belgium) was used for statistical analyses. To test normality of distribution, we used Shapiro- Wilk test.[7]

Data was found to be non-normal (P<0.01) Therefore, the summary statistics have been described in median and Interquartile range. For qualitative data chi square test and for quantitative data Mann-Whitney U test and independent sample t-test was used. A 'P' value of <0.05 was considered statistically significant.

3. Results

The demographic data were comparable in our study (Table 1). The onset of sensory block was delayed in group LM i.e. 102[102-105] sec in comparison to group LT i.e. 69[66-72] sec (p<0.0001). The time to attain peak sensory level was delayed in group LM i.e. 102[102-105] min in comparison to group LT i.e. 1.6[1.5-1.6] min (p<0.0001). Two segment regression time and duration of sensory block were comparable among the groups. (p>0.05) The onset of motor block was delayed in group LM i.e. 93.5[92-65] sec compared to group LT i.e. 60[58-63] sec (p<0.0001). The duration of motor block (min) was less in group LM i.e. 174[168-180] min as compared to group LT i.e. 210[204-210] min (p<0.0001). (Table 2)

Duration of absolute analgesia was extended in group LM 318min (306-324) min compared to group LT 192 min (180-198) min (P<0.001). Duration of postoperative analgesia was also extended in group LM 570 min (540-600) min compared to group LT 357 min (342-360) min (P<0.001). ($) The number of rescue analgesia was more in group LT 3(3-3) as compFigure 1red to group LM 2(1-2). (P<000.1) There was fall in SBP and DBP at 1,3,5 min after giving the spinal anaesthesia in group LT as compared to group LM (p<0.0001). The blood pressure remained lower thereafter but was insignificant. (p>0.05) ($) Figure 3

SpO_2 showed no change throughout the study period. (p>0.05). APGAR score at 1and 5 min after birth of a

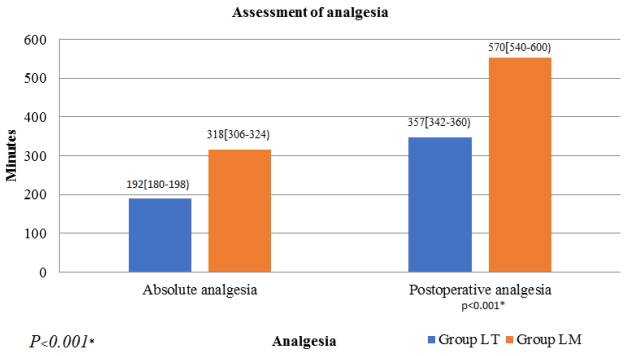

Fig. 1: Assessment of analgesia

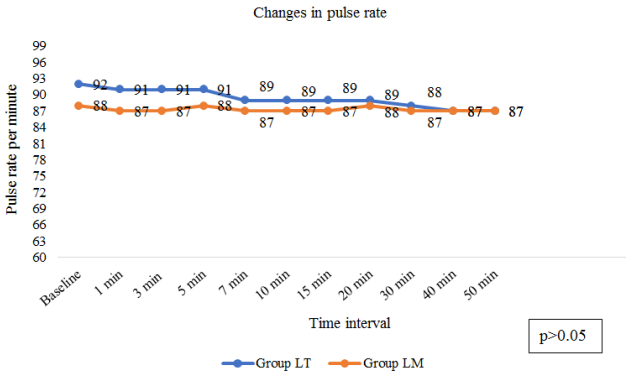

Fig. 2: Changes in pulse rate
(Data presented as mean± standard deviation, independent sample t-test)

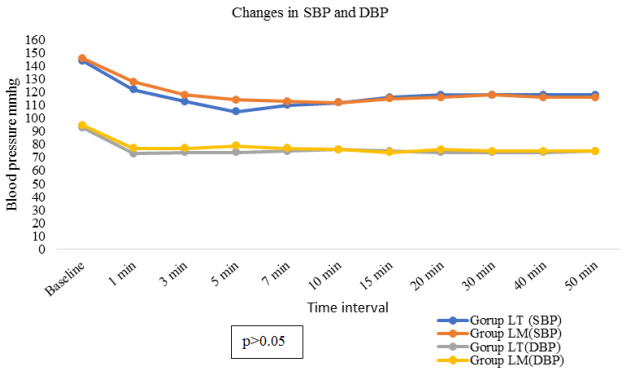

Fig. 3: Changes in systolic and diastolic blood pressure
(Data presented as mean± standard deviation, independent sample t-test)

Table 1: Demographic data

Group	Group LT (n=30)	Group LM (n=30)	P value
Age in years	24(23-26)	24(23-27)	0.53
Weight in Kg	53(51-55)	54(52-55)	0.29
ASA grade II ASA grade III	17 [57%] 13 [43%]	15 [50%] 15 [50%]	0.77
Mean duration of surgery [min]	38(35-42)	40(38-43)	0.12

1. Published: Group LT- levobupivacaine +tramadol, group LM levobupivacaine +MS, Datapresented as median and interquartile range, number(%), not significant,kilogram, American society of anaesthesiologists ' grade.

Table 2: Assessment of spinal block

	Parameter	Group LT [n=30]	Group LM [n=30]	P value
Sensory blockade	Onset [sec]	69[66-72]	102[102-105]	<0.0001*
	Maximum sensory level achieved	T_6 :T_4 28:2	T_6 :T_4 27:3	
	Time to achieve maximum sensory level[min]	1.6[1.5-1.6]	2[1.9-2]	<0.0001*
	Two segment regression time [min]	33[31-35]	32.5[30-35]	0.65
	Duration of sensory block [min]	156[150-180]	168[154.5-180]	0.57
Motor blockade	Onset [sec]	60[58-63]	93.5[92-65]	<0.0001*
	Time to achieve complete block[min]	1.3[1.2-1.4]	1.7[1.7-1.8]	<0.0001
	Duration of motor block[min]	210[204-210]	174[168-180]	< 0.0001*

Valuesare presented as median and interquartile range, group LT- levobupivacaine+tramadol, group LM levobupivacaine+magnesium sulphate,Mann-Whitneytest,*highly significant.

baby was 7.63±0.55 and 7.63±0.49 in group LM and group LT respectively, at 10 minute it was 8.63±0.49 in both the groups. ($p>0.05$). One patient had hypotension in group LM, whereas, four patients had hypotension in group LT. ($p<0.05$). Three patients had nausea/vomiting in group LM, whereas, six patients had nausea/vomiting in group LT. ($p<0.05$).

4. Discussion

Maternal morbidity and mortality are somewhat higher in preeclampsia especially during operative delivery. Various anaesthesia techniques like general anaesthesia (GA) or epidural anaesthesia or spinal anaesthesia are considered to be acceptable and safe for operative delivery, provided due care has been taken to either technique.[1] The risks associated with GA are more in parturients with preeclampsia like difficult airway, failed intubation with risk of aspiration pneumonitis, exaggerated adrenergic response to laryngoscopy and intubation, drug interactions between magnesium and nondepolarizing muscle relaxants (NDMRs) and hampered uteroplacental blood supply. However, epidural or spinal anaesthesia provides relatively stable haemodynamics with reduced requirement of vasopressors compared to normal parturient, thus they also maintain the uteroplacental blood flow.[1,7] In preeclampsia, there is enhanced formation of endothelin and thromboxane plus decreased synthesis of vasodilator like nitric oxide, prostacyclin etc. as a result of generalized vasospasm and endothelial dysfunction. Furthermore, dysfunction of endothelium and vascular smooth muscle cells increases vascular sensitivity to vasoconstricting substances like angiotensin II. These humoral and vascular factors cause vasoconstriction and it remains unaffected by the sympathetic block from SA, but maintain a high vascular tone which limits the decrease in MAP during SA. The increased vascular sensitivity to vasoconstrictors may explain the decreased requirement in vasoconstrictive agents for the treatment of hypotension in preeclamptic patients.[8,9] In addition, spinal anaesthesia allows the parturient to remain awake thus allow her to participate and enjoy the birthing experience.[5,7] The risk – benefit considerations also strongly favour CNB over GA for CS in the setting of severe preeclampsia as long as CNB is not contraindicated.

We used Levobupivacaine (7.5mg) instead of hyperbaric bupivacaine- a pure enantiomer of racemic bupivacaine. The advantages of levobupivacaine are reduced cardiac toxicity and specific effects on sensory rather than motor nerve fibers.[3,10–13] The main limitations of SA are its short duration of action and postoperative analgesia when it is performed only with local anaesthetics. Adding adjuvants not only improves the quality of sensory and motor blockade but also extends the duration of post-operative analgesia and decreases the requirement of systemic analgesics thereafter. Tramadol is a centrally acting analgesic which is devoid

of respiratory depressant effects and neural toxicity. This is because of decreased affinity for μ-receptors compared with morphine. Inhibition of serotonin and norepinephrine reuptake at the spinal cord level contributes to its analgesic effects.[12] Magnesium sulfate, NMDA receptor antagonists causes stimulation of peripheral nociceptive receptors and prevents the induction of central sensitization. Various studies of intrathecal magnesium did not report any signs of neurotoxicity or systemic toxicity like hypotension, arrhythmias weakness or somnolence.[5,14–18] Magnesium sulfate via intrathecal route can be given in the doses like 50,75 and 100 mg. We have used Magnesium sulfate 100 mg intrathecally as it extends the postoperative analgesia, lessens the consumption of analgesics thereafter without increasing side effects.[5,17,19–21]

In our study, demographic data were comparable among the two groups. Onset of sensory block and time to achieve peak sensory level were late in Magnesium group in comparison to Tramadol group *($p<0.0001$).* Various studies also reported that onset of sensory block in the Magnesium group was significantly late than compared group. The reason was – following the addition of magnesium to levobupivacaine, the pH and baricity of the solution differed and was responsible for the late onset.[7,16,18,22] But clinically, this delay is probably insignificant. In our study total 90% of parturients achieved T_6 level following SA. (*$p>0.05$*) Gori et al suggested that levobupivacaine being isobaric in CSF is not affected by gravitational forces, both immediately after the injection and later on. So, with the changes in patient position, level of sensory block will not be altered. While with hyperbaric bupivacaine, level of sensory block may go high unexpectedly even after drug fixation has occurred. So, there are possibilities of late complications like bradycardia and hypotension because of high block.[9] Various authors in their studies found T_4 sensory level in a considerable number of patients as all of them have used hyperbaric bupivacaine which resulted in T_4 level in a significant number of patients.[15,17,18] Two segment regression time and duration of sensory block were comparable among the groups. ($p>0.05$). Onset time of motor block was late in Magnesium group in comparison to Tramadol group ($p>0.0001$) Duration of motor block was extended in tramadol group as compared to magnesium group($p<0.0001$). Other authors had compared magnesium with fentanyl via intrathecal route and they found extended duration of motor block in magnesium group.[5,15,17,18,20] This may be because the half-life of fentanyl is less as compared to magnesium.

Postoperative pain is associated with stress responses with catecholamine release leading to increased morbidity. This may be detrimental in pre-eclamptic patients.[15,17] Duration of absolute and post-operative analgesia were longer in magnesium group in comparison to tramadol group. ($p<0.0001$). (Figure 1) The requirement in number of rescue analgesia were significantly more in the tramadol group than magnesium group ($p<0.0001$). Various studies of intrathecal magnesium also showed similar findings of extended duration of postoperative analgesia and decreased systemic analgesics requirements thereafter.[15,17,18,20,23,24] Our findings further support the role of magnesium sulfate, an NMDA antagonist, as an effective adjuvant for spinal anaesthesia. NMDA receptor activation leads to synaptic plasticity, wind-up phenomenon and central sensitization, which determines duration and intensity of postoperative pain. Magnesium sulfate being NMDA receptor antagonists prevents central sensitization following peripheral nociceptive stimulation[14–16,25] Ko et al. showed an inverse relationship between magnesium concentration in CSF and postoperative analgesic requirement.[16] While Samir EM et al in their study used intravenous versus intrathecal Magnesium sulfate and found that Magnesium sulfate extends postoperative analgesia and decreases opioids requirement.[20] A meta-analysis of intrathecal Magnesium sulfate concludes that the inclusion of 50 to 100 mg of Mg in SA acts as an effective and safe analgesic adjuvant.[18] Tramadol exerts its analgesic activity mainly by inhibiting neuronal reuptake of monoamines, norepinephrine and serotonin. It also exerts its action by being a weak agonist at μ-opioid receptors.[6]

There was no significant change in the mean pulse rate perioperatively in either groups. ($p>0.05$). (Figure 2) There was fall in SBP and DBP at 1,3,5 min following SA and it remained lower thereafter. However, fall in blood pressure was less in magnesium group as compared to tramadol group, which was statistically highly significant($p<0.0001$) but clinically did not require any treatment. (Figure 3) Vasure R et al also observed initial fall in MBP and heart rate from pre-operative value in patients of all the three groups which was statistically significant but clinically not significant.[20] Intravenous Magnesium sulfate is known to cause hypotension when used to treat eclampsia, but not when given via intrathecal route. This is because of the absence of systemic vasodilator effects of intrathecal magnesium.[15,20]

APGAR score was comparable in both the groups. ($p>0.05$) In our study neither mask ventilation nor tracheal intubation was required in new born in either group, which shows safety of intrathecal Magnesium sulfate and tramadol. Literature says that when serum Magnesium level is >15meq/lit, it causes respiratory paralysis when given in eclamptic parturient i.e. 14g Magnesium sulfate loading dose. Here, we used 100mg of Magnesium sulfate intrathecally which was very less as compared to loading dose given intravenously in eclampsia. There are different opinions regarding the predictors of neonatal outcomes, (Neonatal APGAR scores and umbilical arterial blood markers) among two group of patients administered SA or GA. In some studies, APGAR scores was indifferent while

in other studies it was marginally better in the SAB group and transient neonatal depression seen after GA can be avoided by using SAB. [1]

In magnesium group, one patient had hypotension and three patients had nausea. While in tramadol group, four patients had hypotension and six patients had nausea. Patients were treated with IV fluids and vasopressors for hypotension. Injection Metoclopramide was given in patients with nausea-vomiting. Limitation was we could not perform a follow-up for our patients to assess any signs of neurotoxicity or neurologic deficits because of adjuvants intrathecally.

5. Conclusion

We conclude that Magnesium sulfate (100mg) via intrathecal route as an adjuvant to Levobupivacaine in mild pre- eclamptic parturients undergoing CS, delays the onset time and time to achieve maximum sensory level as compared to Tramadol group. It also delays onset time, time to achieve maximum bromage grade for motor block. The duration of absolute analgesia and post-operative analgesia were significantly extended and the number of rescue analgesia was less in Magnesium group. Haemodynamic stability was better in Magnesium group without significant difference in incidence of peri -operative complications. Thus, Intrathecal Magnesium sulfate can be desirable as an adjuvant to Levobupivacaine (0.5%, 7.5mg) in mild preeclamptic parturients undergoing cesarean section compared to tramadol(25mg).

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Dhimar AA, Modh V, Upadhyay MR. Comparison of intrathecal Tramadol and Magnesium sulfate as an adjuvant to Levobupivacaine in mild Pre-eclamptic parturients undergoing caesarean section- A prospective randomized control study.. *Indian J Clin Anaesth* 2019;6(4):481-487.