Maternal and Neonatal Effects of Adding Two Different Doses of Intrathecal Magnesium Sulphate to Bupivacain Fentanyl Spinal Anesthesia in Mild Preeclamptic Patients Undergoing Caesarean Section

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Abstract:Background: Magnesium sulfate (Mg) is an antagonist of N-methyl D Aspartate receptor (NMDA) which improves postoperative analgesia after intrathecal administration for caesarean section helping decrease morbidity, improve patient outcome and facilitates care of the newborn. This study was conducted to evaluate and compare the analgesic efficacy and the maternal and neonatal safety of adding two low doses of intrathecal magnesium sulphate to bupivacaine fentanyl in mild preeclamptic patients undergoing caesarean section. **Method:**By using a double-blinded study design, 60 patients with mild preeclampsia undergoing caesarean section were randomly divided into three groups all received spinal anesthesia with 2ml 0.5% hyperbaric bupivacaine and 25 μg fentanyl either with 1ml preservative free saline in the control group (GC) or 0.5ml of 10% magnesium sulpate (50mg) in the magnesium Group 1(GM_1) or 1 ml of 10% magnesium sulphate (100 mg) in the magnesium 2 group (GM_2). The characteristic of spinal anesthesia (onset and recovery of sensory and motor block and duration of spinal anesthesia), visual analoge scale (VAS), total analgesic consumption, incidence of adverse effects and neonatal outcome (Apgar score and umbilical pH) were recorded for 24hrs after administration of study drugs. **Results:** The time taken for the block to reach T_4 sensory level and time to complete motor block were slower in the magnesium groups compared to control group . Women who received magnesium had greater duration for sensory and motor block. The duration of spinal anesthesia (540.50 VS 359.00 VS 178.00(min)was longest in the (GM_2), next longest in the (GM_1), and least in (GC). VAS score was significantly lower with reduction of total analgesic consumption in groups M_1 M_2 compared to control group with better potentiation of analgesia in M_2 group that showed lowest reduction compared to other two groups . Apgar score was satisfied in all neonates and similar incidence of side effects (hypotension, bradycardia, sedation, nausea and vomiting) found among the three groups. There was a significant reduction in shivering among women received intrathecals magnesium ($P< 0.05$). **Conclusion:** Our study showed that intrathecal magnesium sulphate (50 mg or 100 mg) enhanced bupivacaine fentanyel spinal anesthesia and produced prolonged postoperative analgesia with a greater potentiation in the 100 mg magnesium dose without producing more maternal or neonatal adverse effects.
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1. Introduction

The safety and efficacy of regional anesthesia for preeclamptic patients undergoing caesarean section is established [(1)] Regional anesthesia is preferred for caesarean section since it allows parturient to remain awake and participate in the birth of her baby whilst avoiding the risks of general anesthesia [(2)], but one limitation of spinal anesthesia is the relatively short duration of postoperative analgesia.

To improve the quality of intraoperative anesthesia, postoperative analgesia and aide early ambulation and care of the new born, several agents have been employed such as opioids and n-methyl d-aspartic acid (NMDA) receptor antagonists [(3).] Intrathecal magnesium is one of the agents investigated for this purpose as it is known to inhibit calcium entry into cells and to exhibit noncompetitive blockade of the N-methyl-D-aspartate (NMDA) receptor[(4)].

NMDA antagonists are also involved in decreased catecholamine release associated with sympathetic nerve stimulation during a pain episode this may be essential especially in preeclamptic patients [(5)]. The safety of intrathecal magnesium administration has been evaluated and established as an effective adjuvant to bupivacaine in normal parturients for labor analgesia[(6)] to prolong opioid analgesia with know increase of side effects[(7)].

Aim of the work

The aim of our study was to evaluate and compare analgesic, hemodynamic and neonatal outcome effects of two different doses of magnesium added to intrathecal bupivacain and fentanyl in mild preedamptic women undergoing caesarean section.

2. Patients and Methods:

After approval by the institutional Ethical committee and obtaining informed consents from all the subjects, we enrolled 60 ASA status I or II pregnant women aged 18-50 years old diagnosed with mild preeclampsia (systolic pressure 140-160 mmHg,

diastolic pressure 90-110 mmHg) in a prospective randomized controlled study. Patients were excluded if they had contraindications to regional anesthesia, hepatic or renal impairment, thrombocytopenia, HELLP syndrome, magnesium therapy, fetal distress or if they had received parenteral medications within 1h of spinal injection or had allergies to the study drugs.

The concept of visual analog scale (VAS) from 0 to 10 was introduced before surgery. None of the patients received premedications.

After intravenous infusion of 10ml/kg ringer solution, lumbar puncture for the patients in the left lateral position was performed at L_{2-3} or L_{3-4} inter space with a 25- gauge Quincke spinal needle using a midline approach.

Patients were randomly assigned to one of three treatments in equal numbers with 20 patients in each to receive intrathecal administration of a premixed solution of2ml(0.5%) hyperbaric bupivacain,25 μ g fentanyl with either 1ml preservative free saline in the control group 1 (GC) or 0.5ml preservative – free magnesium sulphate 10% for The magnesium group1 (GM_1) or 1ml preservative- free magnesium sulphate 10% in the magnesium group2 (GM_2) . The total volume of injectate was 3.5ml in all groups, and was prepared by an anesthesia nurse. The same anesthetist performed all the blockwho was unaware of which drug combination was injected. Also the patients and the anesthesiologist collecting data were all blinded to the group. After free flow of cerebrospinal fluid injection of the premixed solution was done over 20s. After drug administration the patient was turned supine with left uterine displacement.

Patients were monitored with continues ECG and pulse oximeter. Heart rate, oxy-haemoglobin saturation (SPO_2), systolic, diastolic and mean arterial blood pressures were monitored non-invasively at the baseline, immediately after block and then every 5 min for the first 20 min, and every 10 min until the end of the surgery.

Hypotension was defined as a fall in systolic pressure > 20% below baseline and was treated by an additional 250ml IV fluid bolus and/or incremental doses of ephedrine 5mg IV. Decrease in heart rate less than 50bpm were treated with incremented doses of atropine 0.25 mg IV.

The level of sensory block, defined as the loss of sharp sensation by using a pinprick test, was recorded bilaterally at the mid-clavicular line until a stable level of block was achieved. Surgery was permitted after T_4 sensory block to pain was achieved. The duration of sensory block defined as the time from intrathecal injection to regression of the sensory block to T_{12}. Motor block was assessed using a modified Bromage score (0= no motor loss, 1 = inability to flex hip, 2 = inability to flex hip and knee, 3= inability to flex hip, knee and ankle 0 = motor recovery). Duration of spinal anesthesia was defined as the period from spinal injection to the time of administration of first rescue analgesic for pain postoperatively.

Neonatal outcome was assessed by Apgar score at 1 and 5 min, umbilical artery pH, and the need for neonatal mask ventilation and tracheal intubation by a pediatrician who was unaware of the study medication.

Pain was, assessed using a visual analog scale (VAS) from 0 to 10 (0 = no pain, 10 = maximum imaginable pain) every 15 min after the block until the end of the surgery and 2, 4, 8, 12, 24hrs postoperatively. If the pain score > 3 it was treated with IV fentanyl 1µg/kg intraoperativly while treated with I.M diclofenac 75µg postoperatively as rescue analgesic.

At the same intervals of time we assessed the pain score we also assessed the incidence of side effects such as sedation, pruritis, nausea and vomiting, shivering and sedation that was measured using the observer's. assessment of Alertness / sedation score [8]. Intravenous ondansertan 4mg was given as rescue medication for vomiting and severe pruritus. Nauseaand vomiting were graded as 0=no nausea or vomiting, 1= nausea no vomiting, 2= both nausea and vomiting, and 3= more than 2 episodes of vomiting in 30min

Statistical analysis

Data were represented as mean±SD for parametric data and median (interquartile range) and Number (percentage) for non parametric data. ANOVA test followed by least standard deviation (LSD) test were used to compare means for parametric data. Kruskal-Wallis test was used to compare group variability for non parametric data.

3. Results

A total of sixty women were enrolled into the study 20 in each group. The three groups were comparable with respect to demographic characteristics, gestational age and duration of surgery (Table 1).

There was a statistically significant difference between the groups in the time needed for the block to reach T_4, Sensory block and regression to T_{12} being more slowly in the two magnesium groups compared to the control group ($p< 0.05$) and also the later (duration of sensory block) was significantly longer in the M_2 group compared to M_1 group(p=0.00) (Table 2, Fig.1). The time needed for complete motor block or recovery was statistically longer in both magnesium groups compared to control group with no difference between both magnesium groups (Table 2).

The time to the first patients demand for rescue analgesic after surgery (duration of spinal anesthesia) was significantly longer in both magnesium groups compared to control group (P=0.00) and significantly

longer in GM2 compared to GM1 (178.00 for GC, 359.00 for GM_1 and 540.50 for GM_2) (Table2- Fig.1)

No patient in the three groups complained of pain during surgery overall 24h VAS score of pain was significantly reduced in both magnesium group compared to control group and significantly reduced for group V_2 patients compared to M1 group patients (Table3). The total amount of postoperative analgesic consumption was significantly lower in the two magnesium groups compared to control group and significantly less in the M2 compared to M_1 group (180. 35 ± 30, 135.32 ± 40, 100. 75 ± 32 for control group, M_1 and M_2 respectively) (Table3).

Baseline haemodynamic parameters (HR, SBP, DBP and MAP) were comparable among the three groups and all decreased significantly 5 min after spinal injection in all groups and significantly decreased in both magnesium groups compared to control group but without significance difference between both magnesium groups. There were no episodes of hypotension or bradycardia requiring treatment among the three groups (Figs. 2,3) .

We did not observe sedation in any of the three groups either intraoperatively or postoperatively. patients free of nausea and vomiting (grade0) were nearly comparable among the studied group while those complained of nausea were significantly increased in M_2 group compared to both groups (0, 2, 5 for control, M_1, M_2 respectively) but grade 2 nausea and vomiting was significantly less in M_2 group compared to other two groups.

Percentage of patients had pruritus in each of the three studied groups was comparable and no patient required treatment (Table4)

About 20% of patients in the control group complained of shivering but no one in the two magnesium groups.

Patient satisfaction was better in the M_1 group compared to control and it was the best in the M_2 group compared to other two groups (Table4)

Neonatal outcome was satisfied in all of the three groups with no statistically significant difference and no baby required mask ventilation or tracheal intubation (Table5)

Table (1): Ppatients data (mean± SD) and (Median (interquartile range))

	GROUP C	GROUPM1	GROUPM2	P
Age (years)	24.60± 4.07	25.30± 4.14	26.00± 5.15	0 .541
Weight (kg)	85.30± 7.16	88.80± 10.00	85.80± 6.24	0 .218
Height (cm)	161.80± 8.31	163.20± 6.33	163.60± 7.51	0 .066
Gestational age (weeks)	39.00(1.00)	39.00(2.00)	39.50(1.00)	____
Duration of surgery (min)	58.1± 3.2	56.3 ± 6.1	60.1 ± 5.4	0.099

No significant changes between the three studied groups using ANOVA and Kruskal-Wallis test.
P value < 0.05 is significant.

Table (2): Characteristics of spinal anesthesia (mean± SD).

	GROUP C	GROUPM1	GROUPM2	P
Time to T4 sensory block (min)	5.60± 0.49 (a) (b)	8.50± 0.50	9.30 ± 0.47	0.22
Duration of Sensory block (min)	156.00± 6.35 (a) (b)	192.50± 4.69 (c)	212.50± 5.26	0.00
Duration of Spinal analgesia (min)	178.00± 4.07 (a) (b)	359.00± 5.48 (c)	540.50± 7.76	0.00
Time to complete motor block (min)	8.6± 1.2 (a) (b)	9.1± 1.1	9.4± 1.2	0.04
Time to complete motor recovery (min)	165.00± 9.3 (a) (b)	205.00± 10	209± 5	0.045

Significant changes between the three studied groups using ANOVA and Kruskal-Wallis test.
P value < 0.05 is significant.

(a) Significant changes between the between GROUP C & GROUP M1
(b) Significant changes between the between GROUP C & GROUP M2
(c) Significant changes between the between GROUP M1 & GROUP M2

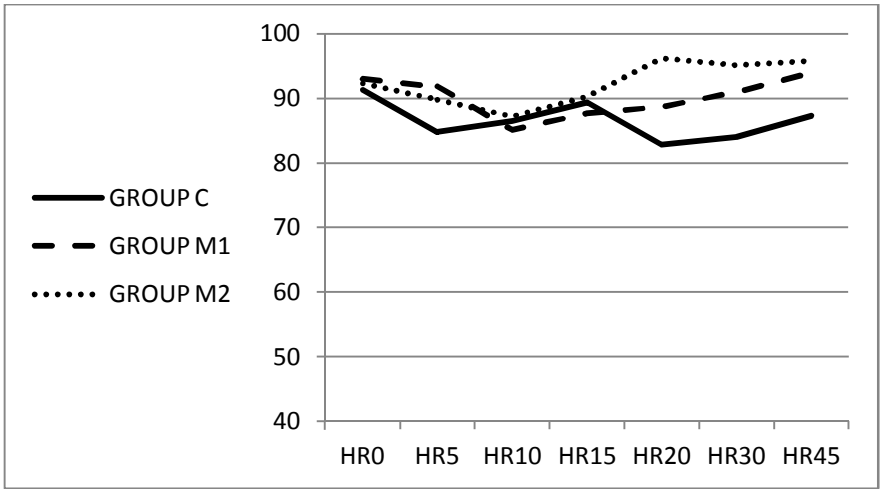

Fig 2: HR= heart rate, (0, 5, 10, 15, 20, 30, 45 min) Intraoperative heart rate, no significant difference between groups and no episodes of bradycardia

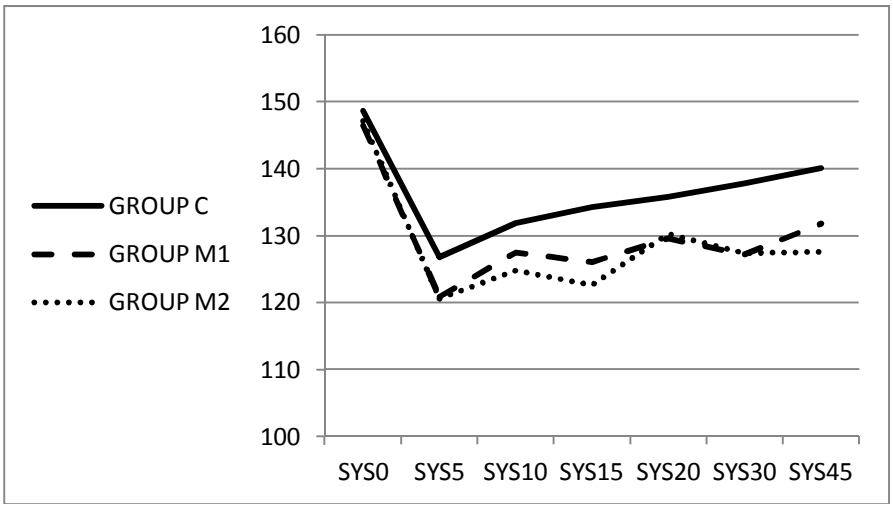

Fig 3: SYS = systolic blood pressure, (0, 5, 10, 15, 20, 30, 45 min)Intra operative systolic blood pressure, significant fall in systolic pressure 5 min after spinal injection compare to baseline in all groups, significant decrease in magnesium groups compared to control group.

Table (3): Postoperative VAS score and analgesic requirement (mean± SD) and (Median (interquartile range)).

	GROUP C	GROUPM1	GROUPM2	P
VAS at first rescue analgesic	6(4-7) [(a) (b)]	3(2-4)	2(2-3)	------
Overall 24hrs VAS score	6(3-7) [(a) (b)]	3(2-5) [(c)]	1(0-2)	------
Number of IM diclofenac dose in 24 hrs	4(3-4) [(a) (b)]	2(1-2)	1(0-1)	------
Total amount of diclofenac (mg) in 24 h	180.35±30 [(a) (b)]	135.32± 40 [(c)]	100.75± 32	0.00

Significant changes between the three studied groups using ANOVA and Kruskal-Wallis test.
P value < 0.05 is significant.

(a) Significant changes between the between GROUP C & GROUP M1
(b) Significant changes between the between GROUP C & GROUP M2
(c) Significant changes between the between GROUP M1 & GROUP M2

Table (4): Incidence of adverse effects and Patients satisfaction score numbers (%)

	GROUP C	GROUPM1	GROUPM2
Nausea and Vomiting:			
Grade 0	16(80%)	15(75%)	14(70%)
Grade 1	0 (0%)	2(10%)	5(25%)
Grade 2	4(20%)	3(15%)	1(5%)
Pruritis:	4(20%)	3(15%)	4(20%)
Sedation:	None	None	None
Shivering:	4(20%)	0 (0%)	0 (0%)
Patients satisfaction score:			
Bad	12(60%)	2(10%)	0 (0%)
Good	8(40%)	10(50%)	10(50%)
Excellent	0 (0%)	8(40%)	10(50%)

Table (5): Neonatal outcome (mean± SD) and (Median (interquartile range))

	GROUP C	GROUP M1	GROUP M2	P
Umbilical Artery pH	7.32±0.01	7.31±0.02	7.31±0.02	0.055
APGAR 0	10.00(1.00)	9.00(0.00)	9.50(1.00)	----
APGAR 5	10.00(0.00)	10.00(0 .00)	10.00(1.00)	----

By ANOVA test & LSD (Post Hoc Tests).P value < 0.05 is significant.

4. Discussion

We showed that magnesium 50 mg or 100 mg added to intrathecal bupivacain and fentanyl for spinal anaesthesia could provide prolonged postoperative analgesia and reduces the postoperative analgesic consumption without serious side effects of nausea and vomiting or neonatal out come affection than those who received only bupivacaine and fentanyl in patients with mild preeclampsia undergoing caesarean section and theses effects showed to be better in the magnesium 100mg dosage regimen producing greater potentiation of analgesia. Previous studies have used the dose of (50mg) neuraxial magnesium sulphate either as intrathecal or epidural dose and reported an increase in duration of analgesia in obstetric and non obstetric populations and found to be safe and effective[9, 10]. In contrast, very high doses of magnesium sulphate produce a transient toxic effect[11].

In our study we used the 50mg dose and compared it with the dose of 100mg magnesium which is a safe intermediate dose as it represents 20% of the dose shown to be nontoxic in dogs[12] in an attempt to improve intraoperative and postoperative conditions and produce greater potentiation of analgesia without increasing the incidence of side effects. Also we choose the mild preeclamptic pregnant women as it has been reported that endogenous opioid analgesic system activates during labor and the early postpartum period[13].

Our study revealed a significant reduction of 24-hrs cumulative VAS score and postoperative analgesic consumption and this was more obvious in the large dose these data are in agreement with **Marzouk *et al.*** who studied the effect of three different doses of intrathecal magnesium[14].

Also these results are in agreements with the fact of the efficacy of magnesium sulphate, an NMDA antagonists, as an effective spinal adjuvant. One of the difficulties with the use of Mg for analgesia is that it penetrates the blood brain barrier very poorly[15] and cerebrospinal fluid (CSF) concentrations of Mg are very tightly controlled even in the presence of established hypermagnesaemia[16]. Therefore it was attractive to consider the administration of Mg via the intrathecal route as this obviates the issue of transfer of the ion across the blood brain barrier without risking the side effects of the large IV doses required.

NMDA receptors are regulated by the physiological concentrations of extracellular Mg ions (Mg_2+). Stimulation of the nociceptive neurons leads to activation of the glutamate postsynaptic receptors. This leads to an inflow of ions, particularly calcium (Ca_2+) into the intracellular space, producing a hyperexcitable state in the neuron. Hyperalgesia is due to the sustained and repetitive activation of afferent fibers leading to a sensitization phenomenon that is the consequence of the facilitation of the neurons of convergence. This process of neuroplasticity involves the formation of facilitated pathways that increase nociceptive sensitivity[17]. This is the consequence of the release of substance P and glutamate in the dorsal horn of the spinal cord and the resultant activation of NMDA receptors[18]. It has also been suggested that the NMDA receptors play an important role in the development of opioid-induced hyperalgesia, and that the use of NMDA receptor antagonists may be beneficial in limiting the development of this phenomenon[19]. NMDA antagonists are also involved in decreased catecholamine release associated with sympathetic nerve stimulation during a pain episode or stress

response to surgery.[5] The role of magnesium in suppressing stress response may be of additional benefit in preeclamptic patients. NMDA antagonists have the potential for inhibiting central sensitization by preventing the excessive stimulation of these pathways in the dorsal horn of the spinal cord.

The time needed to reach the level of sensory block (T_4) and its regression (T_{12}) time were prolonged in both magnesium groups and more pronounced in the 100 mg magnesium group and this is in agreement with the previous experience of **Perry *et al.*** [20] who indicated that fentanyel plus magnesium sulphate (100mg) is hyperbaric compared with CSF and would limit cephaled spread and diminish the usefulness of intrathecal magnesium when injected in the sitting position for labor analgesia so we preferred the lateral position trying to avoid this. These result also reported by **Ozalevli *et al.*** [10] when adding intrathecal magnesium to fentanyl and isobaric bupivacaine and **Malleeswaran *et al.*** [7] who used hyperbaric bupivacaine as we did and both explained this delay by the difference in pH and baricity of the solution containing magnesium. The duration of spinal anesthesia and time to complete motor block or recovery were prolonged in both magnesium group and more favorable in the 100 mg magnesium group. Similar results have been reported by many authors (6, 7, 21) who concluded that the addition of intrathecal magnesium sulphate to bupivacaine and fentanyl spinal anesthesia delayed the onset of sensory and motor blockade but also prolonged the period of anesthesia and reduced postoperative analgesic requirement without inducing adverse effects.

The haemodynamic parameters (HR, systolic, diastolic and mean arterial blood pressure) were significantly decrease in the three groups 5 min after the intrathecal drug administration compared with before intrathecal administration also with significant reduction in both magnesium groups compared to control group but no patient required administration of ephedrine, additional fluids or atropine for hypotension or bradycardia. This may be attributed to the absence of systemic vasodilator effects of spinal magnesium.

We did not find an increased risk of sedation in any of the three groups contrary to the reported increase in the sedation with IV magnesium therapy in preeclampsia [22]. Thus, it is likely that intrathecal magnesium potentiates spinal anaesthesia by a localized action on spinal nociceptive pathways.

In our study the incidence of nausea and vomiting showed no significant difference among groups and this may be related to similar haemodynamic and absence of significant hypotension among groups.

Incidence of post-anaesthetic shivering in control group was 20% as against none in both magnesium groups. Magnesium causes peripheral vasodilatation which probably improves the cutaneous circulation, thus decreasing the incidence of shivering. [23]

The incidence of pruritus was nearly similar among the three groups with no significant difference ($P > 0.05$) which was in agreement with **Mallesswaran *et al.*** [7] showed similar incidence of pruritis when fentanyel 25µg and 50 mg magnesium were added to bupivacain intrathecally.

All of the newborn within the three groups showed a satisfactory Apgar score and umbilical cord pH and none of them needed any intervention in our study and this reinforced the safety of intrathecal magnesium for pain relief in obstetric patients that have been proved by many other authors[7, 9, 10, 24].

In conclusion our study shows that the addition of magnesium sulpahte intrathecally in a dose of 100mg to the combination of bupivacaine and fentanyl in mild preeclamptic patients undergoing caesarean section prolongs the duration of analgesia and reduce the postoperative analgesic requirements in a better quality than 50mg intrathecal magnesium dose without additional maternal or neonatal side effects.

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