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Anesthetic Conversion of Preexisting Labor Epidural Analgesia for Emergency Cesarean Section and Efficacy of Levobupivacaine with or Without Magnesium Sulphate: A Prospective Randomized Study

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Abstract

Background: For pregnant women who require an emergency cesarean section (CS), extending labor epidural analgesia as quickly as feasible to good quality anesthesia is a critical issue. This indicates the presence of functional labor epidural analgesia and reduces the need for general anesthesia. Addition of magnesium increases anesthetic and analgesic qualities of epidural anesthesia.
Objectives: The purpose of this trial was to assess the role of adding magnesium sulfate ($MgSO_4$) with levobupivacaine to speed up the conversion of labor epidural analgesia into enough anesthesia for emergency CS.
Methods: Fifty parturients were randomly assigned to receive 19.5 mL of levobupivacaine 0.5% with either 0.5 mL of normal saline 0.9% (Group I) or 0.5 mL of $MgSO_4$ 10% (Group II) after receiving labor epidural analgesia. We documented the onset of block (loss of pinprick to T6), number of patients needing additional analgesia, the time needed for sensory and motor blockade to recover, and the adverse effects.
Results: The frequency of patients receiving intraoperative supplements was comparable in the study groups (P = 0.491), although the onset of the block was faster in Group II than in Group I (P = 0.000*). Group II took substantially longer to recover from sensory and motor blockade than Group I (P = 0.001* and P = 0.001*, respectively). In both groups, the occurrence of adverse events was similar.
Conclusions: Adding 50 mg of $MgSO_4$ to levobupivacaine 0.5% accelerated the epidural top, and both sensory onset and motor blocks period were prolonged as compared to levobupivacaine alone when extending epidural analgesia for emergency CS.

Keywords: Anesthesia, Cesarean Section, Epidural, Levobupivacaine, Magnesium Sulfate, Obstetric

1. Background

Among the various methods used to relief labor pain, the best one is the neuraxial analgesia (1-3). Epidural technique is a popular efficient approach for delivering adequate pain relief during delivery (4). The epidural catheter can be used to extend an existing block and deliver anesthetic for an emergency cesarean section (CS). Successful conversion is an important indicator of quality and safety since it indicates the presence of functional epidural analgesia and reduces the need for general anesthesia (GA) (5), as well as GA-related side effects (6).

For this purpose, various local anesthetics (LAs) have been used, and the optimal one aimed for a quick onset and good quality of epidural anesthesia (EA) (7). There have been several trials examining the efficacy of different LAs and adjuncts, but none has clarified the optimal solution (8).

Bupivacaine, alone or with different adjuvants, is the most common drug used for CS, and it has a deep and prolonged sensory block (9). Because levobupivacaine is a pure levo-isomer, it has a lower cardiac or neurotoxic effect than racemic bupivacaine. This is crucial when administering high dosages of LA to prolong epidural block to minimize systemic toxicity from inadvertent intrathecal or intravascular administration (10).

Magnesium has analgesic characteristics, which are principally connected to calcium influx modulation and action as a voltage gated antagonist of N-methyl-D-aspartate (NMDA) receptors involved in pain transmission (11-13). Many studies conducted on obstetric anesthesia have searched the efficacy of magnesium sulfate ($MgSO_4$) when combined with spinal anesthesia (14), added to spinal-EA (15, 16). According to these investigations, it increases anesthetic and analgesic qualities while causing no additional side effects, mainly hypotension, which is the most common side effect in spinal anesthesia (17-20).

2. Objectives

This study aimed to detect if using $MgSO_4$ with levobupivacaine could help to speed up the onset of the block while extending pre-existing labor epidural analgesia to enable EA for emergency CS.

3. Methods

This prospective double-blind randomized controlled trial was conducted from August 2020 to June 2021 at Tanta university hospitals in Egypt. The trial was registered at Pan African Clinical Trials after approval of the Institutional Ethics Committee (No:33929/7/20; Tanta University, Faculty of Medicine) (PACTR202007634121137, principal investigator: Radwa Fathy Mansour.; date of approval: July 30, 2020). All participants signed an informed written permission form before starting labor analgesia.

The study included parturients who were in active labor (gestational age > 37 weeks), aged 18 - 35 years, had an American Society of Anesthesiologists physical status II, and admitted for an emergency CS after an established labor EA, and a good fetal condition. Patients were excluded if they had an emergency CS of the first type, multiple pregnancies, a high-risk pregnancy (e.g. preeclampsia, antepartum hemorrhage, diabetes mellitus, body mass index (BMI) $\geq$ 35 kg/m^2), a malfunctioning epidural catheter during the labor (no analgesia after two intra-partum top-up doses), last labor epidural supplementation of less than two hours, hemodynamic instability after a previous top-up, or documented history of allergy to any of the drugs used in the trial.

All participants received a low-dose EA regimen that included a bolus dose of 1 mL fentanyl (50 μg) mixed to 9 mL 0.125% levobupivacaine and a subsequent infusion of levobupivacaine 0.125% with fentanyl (2 μg/mL) at a rate of 10 mL/h. To obtain the desired degree of labor analgesia, an extra supplementation of 5 mL levobupivacaine 0.125% bolus was given if necessary (up to T10).

Parturients were moved to the operating room, and standard monitoring such as electrocardiography, pulse oximetry, and non-invasive blood pressure were used once the choice for emergency CS was reached.

The patients were randomly allocated into two equal groups of 25 patients each at a ratio of 1:1 to receive 19.5 mL of levobupivacaine 0.5% with either 0.5 mL of normal saline 0.9% (Group I) or 0.5 mL of $MgSO_4$ 10% equivalent to 50 mg (Group II) using computer-generated randomization numbers enclosed in sealed opaque envelopes. To ensure blinding, the anesthetic mixtures were prepared in two identical syringes labeled as syringes 1 and 2 by an anesthesiologist who had no further involvement in the study, while injection of the top-up epidural anesthetic doses and recording of outcomes were done by a different investigator who was unaware of group allocation. The LA was then given in aliquots over three minutes through the epidural catheter following negative aspiration; then, the established levels of sensory and motor blocks were tested (0 = can raise extended leg off bed; 1 = can bend knees; 2 = can bend ankles; 3 = unable to bend knees or ankles).

The interval between the completion of the epidural top-up injections and verification of the block to pinprick perception up to the T6 dermatome is described as the onset of block (our primary outcome). Testing for the level of blockade was performed at 3-minute intervals; if inadequate anesthesia was reported after 20 minutes, a supplementary top-up dose of 5 mL of lidocaine 2% was given and reassessment was done 10 minutes later. Absence of adequate T6 sensory block after 30 minutes was considered as block failure warranting the conversion to general anesthesia, and the patient was withdrawn from the study.

During surgery, further epidural increments (5 mL of lidocaine 2%) were supplied if breakthrough pain was indicated by a visual analogue scale (VAS) > 3 or if any patient's discomfort was experienced, and the number of patients who required supplemental analgesia was documented. Sedation levels were also measured every 10 minutes on a four-point scale (1 = Awake and attentive, 2 = Drowsy, responsive to verbal stimuli, 3 = Drowsy, arousable to physical stimuli, 4 = Unarousable).

Hypotensive episodes were treated with an intravenous (IV) fluid bolus and ephedrine 5 mg increments. Atropine 0.5 mg IV bolus was used to treat bradycardia. Patients were monitored for 24 hours postoperatively. The initial onset of analgesic request and a Bromage score of 0 were used to identify sensory and motor block recovery. The time from administering the study medications until recovery was assessed and recorded by a trained nurse every 30 minutes. In addition, the incidence of adverse events 24 hours postoperatively (e.g., nausea, vomiting, and sedation level $\geq$ 2) was recorded.

3.1. Statistical Analysis

The onset of the sensory blackout was our primary outcome variable. According to prior research, the mean $\pm$ standard deviation (SD) time to start the sensory block of epidural levobupivacaine in extending labor analgesia for emergency CS was 155.83 minutes (8, 21). The sample size calculation found that each group needed a minimum of 23 patients to detect a clinically significant onset time difference of 5 minutes between groups at an error rate of 0.05 and an 80% power of the study. Assuming a 10% dropout rate, each group included 25 members. For statistical analysis, the statistical software Minitab® 16 (Minitab, Inc, LLC, State College, Pennsylvania) was used. The Kolmogorov-Smirnov test was used to ensure that the data was normal. Numerical data was compared between the two groups using Student's independent *t*-test for data with normal distribution or Mann–Whitney U test if the data did not have normal distribution. Patients' numbers and percentages (%) were used to express categorical variables, which were compared using the chi-square test or Fisher's exact test when suitable. Significance was defined as $P < 0.05$.

4. Results

In total, we included 93 eligible parturients in this study. Seventeen patients did not comply with our inclusion criteria (nine patients were preeclampsia, four patients had their last epidural top-ups less than 2 h, three patients had BMI $\geq$ 35, and one patient was grade 1 emergency cesarean delivery), and 26 patients declined to take part in the research. Fifty patients were enlisted and evenly distributed across the study groups. Two of the patients in group I and three of the patients in group II did not reach the T6 sensory level, and were excluded from analysis (Figure 1).

The demographic features of the studied participants, as well as the indications and duration of CS, did not differ between the two groups (Table 1). Both groups were also similar regarding the details of the already established EA (Table 2).

In comparison to Group I, the time necessary to block the pinprick sensation up to T6 was significantly shorter in Group II (P = 0.000*). Furthermore, the sensory block level and the degree of motor blockade at the start of surgery were comparable in both groups (P = 0.636 and P = 0.384, respectively). In terms of the number of patients getting intra-operative supplements or the neonatal Apgar scoring, no significant differences were detected between the groups (P = 0.794, 0.491, 0.812 at 1 min, and 0.681 at 5 min, respectively). Nevertheless, Group II experienced a considerably longer duration of analgesia than group I, as well as a longer period for motor block regression to a Bromage score of 0 (P = 0.001* for all) (Table 3).

The two groups had equal rates of adverse events such as hypotension, vomiting, bradycardia, and nausea. There were no patients in either group with a sedation level of $\geq$ 2 (Table 3).

5. Discussion

During the management of emergency CS, short time from decision of delivery to induction of anesthesia can influence the mode of anesthesia. Although spinal anesthesia is popular in this situation, EA should be utilized if labor analgesia is established prior to an emergency CS.

In our study, during the conversion of EA to surgical anesthesia for emergency CS, the addition of $MgSO_4$ (50 mg) to epidural levobupivacaine 0.5% was investigated. The addition of $MgSO_4$ as an adjuvant provided a sensory block with a rapid onset and a lengthy duration, and it extended the duration of the motor block. In addition, it reduced the number of patients who needed supplemental dose of anesthesia intra-operatively. We also considered the consequences of adding $MgSO_4$; there were no harms to the newborn, and no differences were observed in terms of maternal adverse effects.

The dose of $MgSO_4$ in this study was based on a study by Ghatak et al. (22), demonstrating that adding 50 mg of $MgSO_4$ to epidural bupivacaine resulted in rapid onset of anesthesia without complications.

The findings of our investigation are comparable to those by Hasanein et al. (16), reporting that adding $MgSO_4$ to epidural bupivacaine and fentanyl for labor analgesia reduced the breakthrough pain and had a longer duration of action.

Also, our findings are in line with those of Elsharkawy et al. (23), reporting that adding $MgSO_4$ to EA (in elective CS) had fast onset and prolonged duration of action with improved analgesic profile. Although they used higher dose of $MgSO_4$ (500 mg) than our study, there were no neonatal or maternal complications. Ko et al. (24) demonstrated that large intravenous dose of $MgSO_4$ did not increase its concentration in cerebrospinal fluid and had no postoperative analgesic effect. Also, Sun et al. (25) showed that a bolus dosage of magnesium (500 mg) administered via epidural injection produced a spinally mediated analgesic effect with no systemic adverse effects (26).

Irrespective of the type of surgery, some previous studies (27-30) demonstrated that addition of magnesium to bupivacaine and/or opioid resulted in accelerating the onset of sensory block. Moreover, some other studies (27, 28) showed that the addition of magnesium to levobupivacaine hastened the onset of motor block, prolonged the duration of motor and sensory block, and had no major side effects. In contrast to our results, Ahmed et al. (29) found that magnesium showed more incidence of pain with injection and Ranjan et al. (30) reported that adding magnesium to levobupivacaine resulted in no significant differences in the onset of motor block and the length of sensory and motor block.

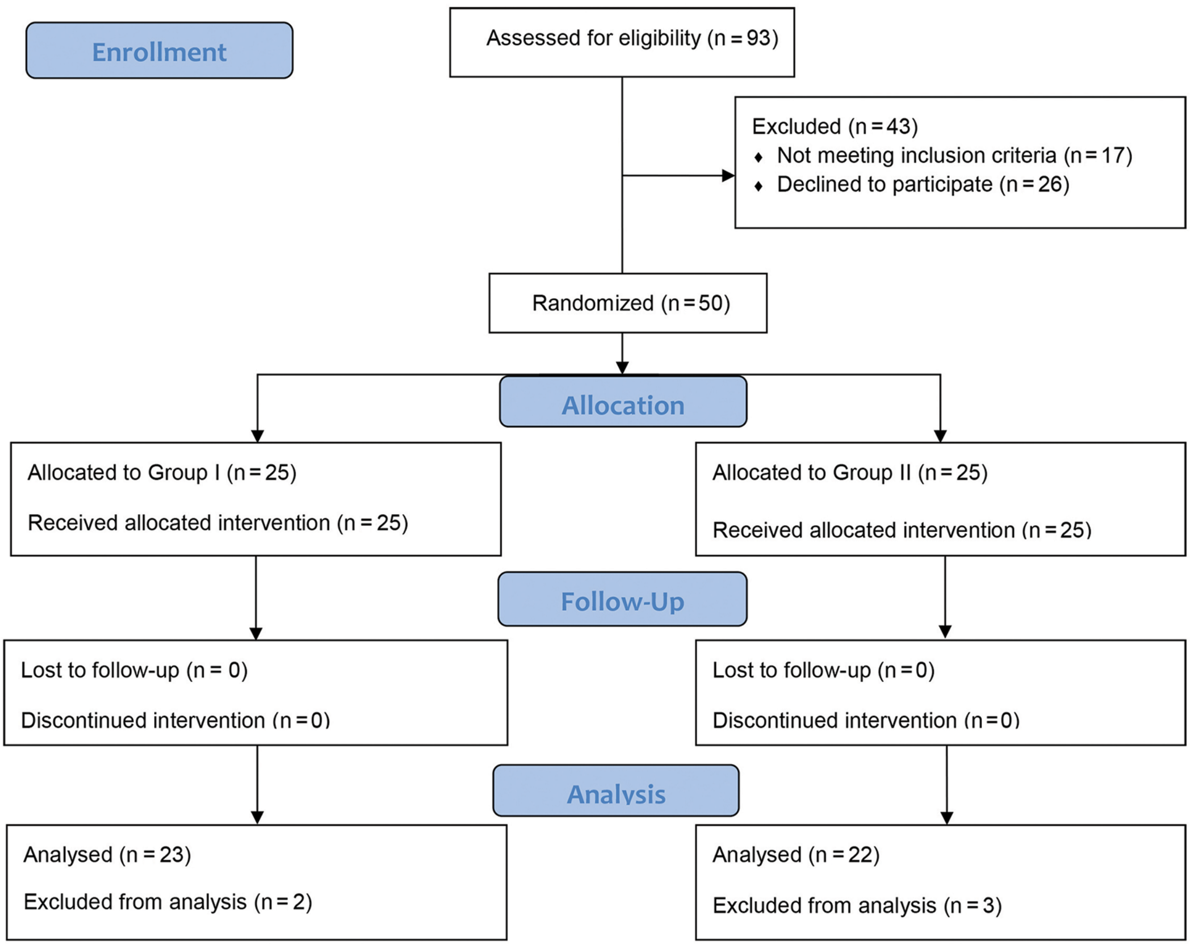

Figure 1. Contrast flow diagram of participants through each stage of the randomized trial.

Table 1. Demographic Characteristics and Duration of Surgery in the Studied Parturients [a]

Variables	Group I (n = 23)	Group II (n = 22)	P-Value [b]
Age (y)	27.39 ± 3.83	28.18 ± 4.02	0.504
BMI (kg/m^2)	28.01 ± 3.29	27.12 ± 3.71	0.400
Gestational age (weeks)	38.87 ± 1.06	38.500 ± 0.913	0.216
Parity; nulliparous/multiparous	4 (17.4)/19 (82.6)	5 (22.7)/17 (77.3)	0.722
Duration of surgery (min)	38.65 ± 6.87	40 ± 7.33	0.528

[a] Data are expressed as mean ± SD or patient's No. (%).
[b] $P < 0.05$ is significant. BMI, body mass index.

Similar to our results, Rekha et al. (31) evaluated orthopedic procedures, and found that adding 50 mg of magnesium to epidural ropivacaine shortened the onset of sensory and motor block while it had no effects on the duration of sensory block and no significant adverse effects.

Other studies used different doses of magnesium as an adjuvant to opioids and/or LAs of different types, and they reported results similar to our study. Elsharkawy et al. (23), in preeclampsia patients receiving elective CS, added 500 mg of magnesium to spinal bupivacaine. Gupta et al. (32) utilized 500 mg of magnesium as an adjuvant to epidural ropivacaine and fentanyl in labor analgesia. Radwan et

Table 2. Characters of Labor Analgesia [a, b]

Variables	Group I (n = 23)	Group II (n = 22)	P-Value [c]
Duration of labor analgesia (h)	6.83 ± 1.40	6.64 ± 1.62	0.677
Time since last top-up dose (min)	189.8 ± 44.6	200.0 ± 46.1	0.454
Pre-sensory level (%)			0.725
T7	1	0	
T8	3	3	
T9	2	3	
T10	5	5	
T11	3	6	
T12	3	3	
L1	5	2	
L2	1	0	
Pre-motor level	0 (0 - 1)	1 (0 - 1)	0.665
Pre –VAS	2 (2 - 3)	2.5 (2 - 3)	0.785

Abbreviation: VAS, visual analogue score.
[a] Pre-sensory and pre-motor level refer to the sensory and motor levels before initiating the epidural anesthesia. Pre-VAS refers to the pain intensity before initiating the epidural anesthesia.
[b] Data are expressed as mean ± SD, median (interquartile range) or patient's No. (%).
[c] $P < 0.05$ was considered significant.

al. (33), in old patients undergoing spine operations, compared 50 mg of magnesium to fentanyl as an adjuvant to epidural levobupivacaine with continuous infusion intraoperatively. All these studies found that adding magnesium to the mix accelerated the onset of motor and sensory block and lengthened the block's duration. Despite using different doses of magnesium, there were no maternal, neonatal, or geriatric adverse outcome.

Some clinical trials compared magnesium with other adjuvants to EA. Hanoura et al. (34) evaluated adding dexmedetomidine to EA in CS; there were no variations in the block onset or the duration of the block, but the duration of sensory block was prolonged and there were no maternal or fetal adverse consequences. Also, Shahi et al. (35), in orthopedic surgeries, compared magnesium and dexmedetomidine as an adjuvant to EA. They found that shorter time to achieve sensory block was obtained by adding dexmedetomidine (but it was not statistically significant), while there was prolongation of sensory and motor block. The delayed motor recovery may be inappropriate for postpartum females who are in need for early ambulation and care of the baby. There was also a significant variation in the incidence of bradycardia (not hypotension). So, due to bradycardia and the potential risk of hypotension, the benefit-risk ratio must be balanced when dexmedetomidine is added to EA in CS. Meanwhile, epidural magnesium seems to be a good alternative to dexmedetomidine.

In contrast to these findings, Hanoura et al. (36) showed that neither the onset of the block nor the recovery of the motor block were affected by epidural dexmedetomidine in CS. However, it prolonged the sensory block, enhanced the quality of intraoperative and postoperative analgesia, while maintaining a low degree of arousal sedation without causing major maternal or neonatal side effects. Also, Imani et al. (37) demonstrated that combination of intravenous dexmedetomidine with non-opioid analgesics for pain management in CS did not have hemodynamic complications.

In lower limb and abdominal procedures, compared to epidural clonidine (22), epidural magnesium allows for a rapid onset of surgical anesthesia with no side effects, while adding clonidine prolongs anesthesia duration along with significant sedation. Similar results were obtained by Bajwa et al. (38), as they found that epidural clonidine in CS resulted in shorter onset of analgesia with a longer duration, but with more bradycardia and hypotension occurrence, which may be detrimental for parturients. Rajabi et al. (39) reported that when intravenous infusion of magnesium or clonidine were used in combination with GA in CS, once at the time of the induction, they had favorable hemodynamic and anesthetic profile with no risk to the neonate.

This study had some limitations. First, different doses of $MgSO_4$ should be used to know the optimum dose to be used without significant side effects. Second, the syner-

Table 3. Operative Data and Adverse Events

Variables	Group I (n = 23) [a]	Group II (n = 22) [a]	P-Value
Time to block at level T6 (min)	19.17 ± 4.46	13.82 ± 3.39	0.000 [b]
Number of patients who needed top-up to reach level T6, No. (%)	6 (26.08)	1 (4.55)	0.096
Sensory level at the start of surgery (%)			0.636
T1	0	1	
T2	2	5	
T3	5	5	
T4	7	4	
T5	7	5	
T6	2	2	
Motor block at the start of surgery	2 (2 - 3) R: 1 - 3	3 (2 - 3) R: 1 - 3	0.384
Number of patients needing supplemental intra-operative analgesia (%)	7	4	0.491
Duration of analgesia (min)	130.83 ± 27.66	160.77 ± 26.4	0.001 [b]
Time to motor recovery (min)	119.05 ± 7.67	126.09 ± 5.74	0.001 [b]
Apgar score			
1 min	9 (9 - 10)	9 (9 - 10)	0.812
5 min	10 (10 - 10)	10 (9 - 10)	0.681
Adverse events (%)			
Hypotension	6 (26.1)	8 (36.4)	0.530
Bradycardia	2 (8.7)	3 (13.6)	0.665
Nausea	7 (30.4)	5 (22.7)	0.738
Vomiting	5 (21.7)	3 (13.6)	0.699
Sedation ≥ 2	0 (0)	0 (0)	-

Abbreviation: R, range.
[a] Data are expressed as mean ± SD, median (interquartile range), or patient's No. (%).
[b] $P < 0.05$ was considered significant.

gistic effect of intravenous and epidural $MgSO_4$ should be studied, which may speed up the onset of action.

5.1. Conclusions

To conclude, adding 50 mg of $MgSO_4$ to levobupivacaine in the epidural catheter during the epidural labor analgesia to anesthesia conversion for an emergency CS significantly accelerated the onset of sensory block and delayed the recovery of both sensory and motor block, without any major maternal or fetal side effects.

Footnotes

Authors' Contribution: Study concept and design: R. F. M. and M. R. E.; Acquisition of data: M. R. E. and R. F. M.; Analysis and interpretation of data: M. R. E. and T. M. N; Drafting of the manuscript: M. R. E.; Critical revision of the manuscript for important intellectual content: T. M. N. and R. F. M.; Statistical analysis: T. M. N.; Administrative, technical, and material support: T. M. N. and M. R. E.; Study supervision: T. M. N. and R. F. M.

Clinical Trial Registration Code: PACTR202007634121137.

Conflict of Interests: The authors declare no conflicts of interest.

Data Reproducibility: The data presented in this study will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

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