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Effect of Adding Dexmedetomidine versus Magnesium Sulfate to Intrathecal Bupivacaine on Maternal Hemodynamics during Elective Cesarean Section: a Randomized Controlled Trial

Ahmed Talaat[1], Mohamed F. Mostafa[1], Hanan Galal[2], Zein El-abden Z. Hassan[1], Golnar M. Fathy[1] and Ahmed M. Abbas[3]*

[1]Department of Anesthesiology and intensive care, Assiut University, Assiut, Egypt

[2]Department of Clinical Pathology, Assiut University, Assiut, Egypt

[3]Department of Obstetrics and Gynecology, Assiut University, Assiut, Egypt

***Corresponding author: Dr Ahmed M. Abbas,** Email: bmr90@hotmail.com

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Abstract

Objective: The current study aims to compare the effect of adding dexmedetomidine intrathecally 5 µg and magnesium sulfate 50 mg with hyperbaric 0.5% bupivacaine for spinal anesthesia versus hyperbaric 0.5% bupivacaine given intrathecally alone for elective cesarean section (CS) on maternal hemodynamics. The aim of adding adjuvant is to augment the analgesia produced by intrathecal local anesthetics and to reduce their adverse effects**.**

Methods: A randomized double-blind controlled trial; Clinical Trials.Gov (NCT03067896) was carried out in the operating room of a tertiary University Hospital included 90 patients (ASA) physical status I-II scheduled for elective CS**.** Patients were randomly divided into three groups: **Group C:** received intrathecal hyperbaric bupivacaine 12.5mg in 2.5ml + 0.5 ml saline. **Group D:** received intrathecal hyperbaric bupivacaine 12.5mg in 2.5ml with Dexmedetomidine 5 µcg in 0.5 ml normal saline. **Group M:** received intrathecal hyperbaric bupivacaine 12.5mg in 2.5ml with Magnesium sulfate 50 mg in 0.5 ml normal saline. The study outcome included the differences in pre, intra, and postoperative heart rate, blood pressure among the study groups.

Results: Ninety Patients were divided randomly in this study. No statistical significant difference between all study groups regarding the sociodemographic and clinical criteria. No statistically significant differences were observed between the different groups at different times regarding the heart rate (P>0.05). Similarly, no statistically significant differences were observed between the different groups at different times regarding blood pressure measurements (P>0.05).

Conclusions: Low-dose of dexmedetomidine (5µg) intrathecally during CS has no significant adverse effects on the maternal hemodynamics when compared with magnesium sulphate.

Keywords: Dexmedetomidine; Magnesium sulfate; Intrathecal bupivacaine; Cesarean section

Introduction

Regional anesthesia (RA) has become more popular in cesarean deliveries (CD) because most of pregnant women prefer being awake during the birth process. In addition, RA is safer method than general for the mother and her newborn. In spinal anesthesia; local anesthetics alone may not be enough for an effective postoperative analgesia and hemodynamic stability of the patient which is crucial during cesarean section (CS). Therefore, many adjuvants have been used to augment the analgesia produced by intrathecal local anesthetics and to reduce their adverse effects [1].

Various intrathecal adjuvants to local anesthetics have found to improve the quality and extend duration of spinal block. Prolongation of duration of spinal block is desirable both for long procedures and for postoperative pain relief. Efficacy and safety of intrathecal magnesium as analgesic adjuvant has been tested by several clinical trials in recent years [1].

Antinociceptive effect of magnesium appears to be relevant for the management of chronic and post operative pain [2]. These effects are primarily based on regulation of calcium influx in to the cell. Magnesium blocks calcium influx and non competitively antagonizes NMDA channels [3]. NMDA receptor signaling plays an important in determining the duration of acute pain. Addition of magnesium to spinal anesthesia improved postoperative analgesia in orthopedic setting addition of intrathecal magnesium sulfate to 10 mg bupivacaine plus 25µg fentanyl prolonged spinal anesthesia in patients undergoing lower extremity surgery [4].

Dexmedetomidine is a highly selective 2-adrenergic agonist which has been used as pre-medication and as an adjuvant to general anesthesia [5]. Dexmedetomidine have several beneficial actions during perioperative period. They decrease sympathetic tone with attenuation of the neuroendocrine and hemodynamic response to anaesthesia and surgery, reduce anesthetic and opioid requirement, cause sedation and analgesia.

Dexmedetomidine was first introduced into clinical practice as a short term intravenous sedative in intensive care [6]. Like any other adjuvant; dexmedetomidine is not free from adverse effects. Use of dexmedetomidine is often associated with a decrease in heart rate and blood pressure [7]. Dexmedetomidine was used to enhance the analgesic property of local anesthetics like lidocaine bupivacaine and ropivacaine. In vivo and in vitro studies indicated that these local anesthetics had significant neurotoxicity [8]. Dexmedetomidine showed protective or growth promoting properties in tissues, including nerve cells from cortex. Intrathecal dexmedetomidine has a neuroprotective effect similar to methylprednisolone [9].

The purpose of this study is to compare the effect of adding dexmedetomidine intrathecally 5 µg and magnesium sulfate 50 mg with hyperbaric 0.5% bupivacaine for spinal anesthesia versus hyperbaric 0.5% bupivacaine given intrathecally alone for elective CS on maternal hemodynamics.

Materials and Methods

The current study was a prospective randomized controlled trial (RCT), conducted in a tertiary University Hospital between the 1st of January 2016 and the 30th of December 2016. The Institutional Research Ethical Review Board approved the study. This trial was registered at Clinical Trials.Gov (NCT03067896).

All women scheduled for elective CS were invited to participate. All eligible participants included in the study signed a written informed consent before participation after explaining the nature of the study. We included women aged 18-42 years old, pregnant in singleton pregnancy with gestational age > 38 weeks and American society of anesthesiologists (ASA) physical status I-II.

We excluded women with history of cardiac, liver or kidney diseases, allergy to amide local anesthetics or medications included in the study, any neurological problem, contraindication of regional anesthesia, and evidence of intrauterine growth restriction or fetal compromise. Finally, cases with failed or unsatisfactory spinal block were also excluded.

The study was double-blind randomized using a computer-generated randomization program. Neither the investigator nor the participant was aware of the group allocation or the drug used. The drugs used were prepared by one of the supervisor anesthesiologists (not included in the procedure, observation or in the data collection).

Ninety Patients were concerned to participate randomly in this study and were assigned to 3 groups. Each group consisted of 30 patients.

Group C: received intrathecal hyperbaric bupivacaine 12.5mg in 2.5ml + 0.5 ml saline.

Group D: received intrathecal hyperbaric bupivacaine 12.5mg in 2.5ml with Dexmedetomidine 5 µcg in 0.5 ml normal saline

Group M: received intrathecal hyperbaric bupivacaine 12.5mg in 2.5ml with Magnesium sulfate 50 mg in 0.5 ml normal saline.

Standard preoperative data were collected prospectively for all patients undergoing elective cesarean section in our institution. All operations were carried out by one team of surgery and anesthesia was standardized in all patients. Assessment of the patient during preoperative period to form baseline data allowed to be compared with intraoperative and postoperative data. It consisted of two parts:

Part I: - Assessment of the sociodemographic patient's profile: to assess the patient's profile as patient's name, age, type of surgery and ASA physical status.

Part II: - Assessment of vital signs and electrocardiogram (ECG).

Preparation

Patient in the holding area, baseline vital signs were recorded (blood pressure, heart rate, arterial oxygen saturation, respiratory rate). Eighteen gauge IV cannula was inserted; no premedication drugs were given to all patients. Ringer lactate (15ml/kg) was infused over 30 min after careful sterilization; spinal anesthesia was carried out by 25 gauge spinal needle in the sitting position at L2-L3 OR L3-L4 level through a midline approach. After intrathecal injection, patients were positioned in supine position with left uterine displacement, and oxygen (5 L /min) was supplied by face mask.

Vital signs (heart rate, systolic, diastolic, mean blood pressure, and arterial oxygen saturation) were recorded at 2 min interval intra-operatively till 15 min duration, and then every 5 min till the end of surgery. In the post anesthesia care unit (PACU) every 15 min for 3 hours then at 30 min interval for 3 hours .

Hypotension was defined as decrease in systolic blood pressure >20% of the baseline value or systolic blood pressure <90% mm Hg. Hypotension was treated by intravenous boluses of 6 mg ephedrine and crystalloid fluid. Bradycardia was defined as HR< 50 beat /min and was treated by 0.4-0.5 mg atropine. The need of ephedrine, IV fluids or atropine was recorded by time and dose.

The primary outcome of the study was the difference between pre and postoperative HR. the secondary outcomes included the difference between pre and postoperative BP, (SaO2) saturation and side effects of the study medications.

Statistical Analysis

Data were collected and analyzed by computer program SPSS (SPSS Inc., Chicago, Illinois, USA) version 23. Data expressed as means, standard deviations, ranges, numbers and percentages. T-test or Mann-Whitney test if necessary were used to determine significance for numeric variable. Chi-Square or Fisher exact test was used to determine significance for categorical variables. P value <0.05 was considered statistically significant.

Results

No statistical significant difference between all study groups regarding the sociodemographic and clinical criteria as shown in Table 1. Comparisons of pre & Intra-operative (First 15 min and Second 15min) arterial saturation (SaO2) between the study groups showed non-statistically significant difference (P>0.05) (Table 2).

Table 1: The socio-demographic characteristics of the study participants in the three.

Variables	Group C (n=30)	Group D (n=30)	Group M (n=30)	P-value
Age (years)	28.90 ± 5.81	31.53 ± 4.84	29.35 ± 6.21	0.372
Residence:				
• Rural	27(90.0%)	26(86.67%)	27(90.0%)	0.271
• Urban	3(10.0%)	4(13.33%)	3(10.0%)	
Education:				
• Illiterate	18(60.0%)	18(60.0%)	16(53.33%)	0.724
• Primary	4(13.33%)	3(10.0%)	5(16.67%)	
• Secondary	5(16.67%)	4(13.33%)	3(10.0%)	
• University	3(10.0%)	5(16.67%)	6(20.0%)	
Occupation:				
• House wife	24(80.0%)	25(83.33%)	26(86.67%)	0.386
• Work	6(20.0%)	5(16.67%)	4(13.33%)	
Gestational age	38.90 ± 1.18	37.82 ± 1.15	38.50 ± 1.13	0.223
Gravidity:				
• Primigravida	4 (13.33%)	5 (16.67%)	6 (20.0%)	0.184
• Multigravida	26 (86.67%)	25 (83.33%)	24 (80.0%)	

Table 2: Pre &Intra-operative SaO2 in study groups.

Variables	Group C (n=30)	Group D (n=30)	Group M (n=30)	P-value
SaO_2 _ pre-op	99.60 ± 0.30	99.01 ± 0.61	99.2 ± 0.7	0.183
SaO_2				
• First 15 min	99.05 ± 0.71	99.33 ± 0.52	99.66 ± 0.25	0.639
• Second15 min	99.44 ± 1.14	98.80 ± 3.11	97.00 ± 2.27	0.421

Figure 1 shows the pre, intra and postoperative follow up of HR readings in the three study groups. No statistically significant differences were observed between the different groups at different times (P>0.05).

Similarly, Figures 2, 3, 4 show the pre, intra and postoperative follow up of SBP, DBP and mean BP readings respectively in the three study groups. Again, no statistically significant differences were observed between the different groups at different times (P>0.05).

Side effects in three study groups showed non-statistically significant difference (P>0.05) between different groups as shown in Table 3.

Discussion

Pain during childbirth has been described by women as severe and

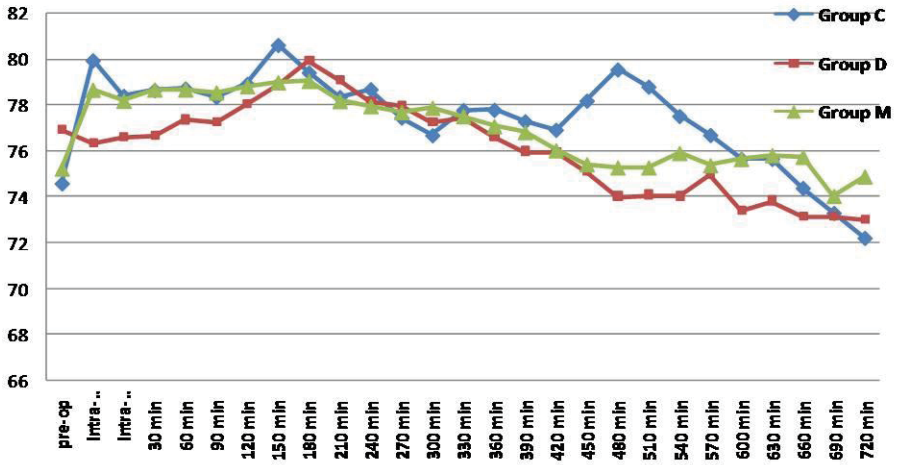

Figure 1: Pre, Intra and Postoperative follow up of heart rate recordings in the study groups.

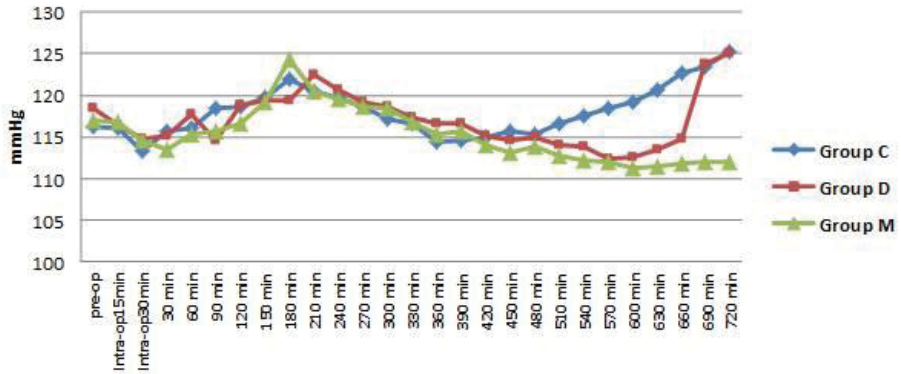

Figure 2: Pre, Intra and Postoperative follow up of systolic BP recordings in the study groups.

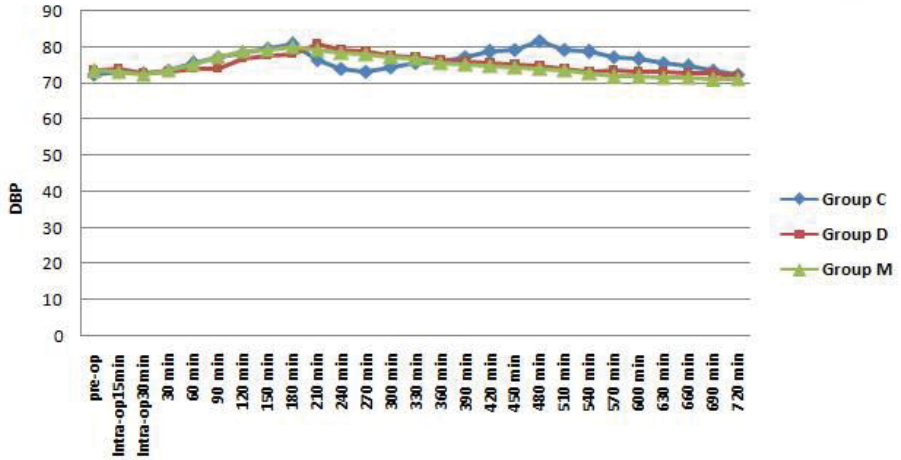

Figure 3: Pre, Intra and Postoperative follow up of diastolic BP recordings in the study groups.

Table 3: Side effect in study groups.

Variables	Group C (n=30)	Group D (n=30)	Group M (n=30)	P-value
Backache	6 (20.0%)	4 (13.33%)	5 (16.67%)	
Headache	3 (10.0%)	2 (5.0%)	3 (10.0%)	0.593

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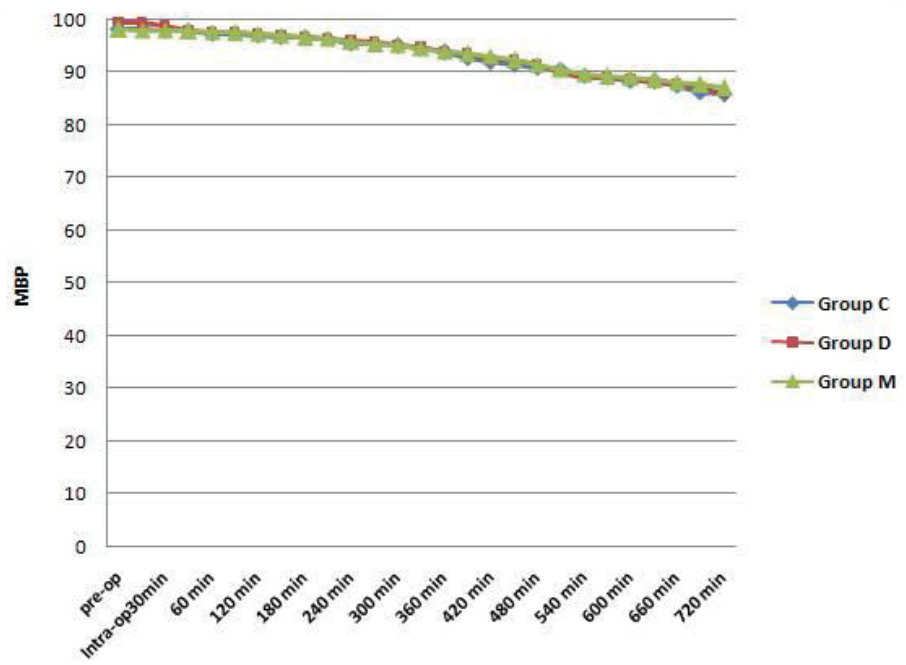

Figure 4: Pre, Intra and Postoperative follow up of mean BP recordings in the study groups.

frequent; these parturient especially those in the developing countries have few or no options for labor pain relief during childbirth. Parenteral opioids are the most frequently prescribed agents for women in labor in many poor resource settings [10]. Pain relief not only provides patient's comfort, but also attenuates the release of stress hormones, whose actions can draw from the parturients' reserves as well as depriving the fetus of oxygen and nutrients [11].

The advantages of spinal anesthesia in CS include the rapidity of onset and reliability, with minimal hemodynamic changes and motor block. The current practice in modern anesthesia is to add small doses of adjuvants to local anesthetics to fasten the onset time, improve quality of intra-operative anesthesia, prolong analgesia and decrease the complications associated with intrathecal administrations of high dose of hyperbaric bupivacaine alone. Such adjuncts include the use of fentanyl, sufentanil, morphine, clonidine, ketamine, dexmedetomidine, magnesium sulfate, neostigmine, ketamine and midazolam [10].

In our study we compared the effect of adding dexmedetomidine or magnesium sulfate as adjuvants to intrathecal bupivacaine on the maternal hemodynamics in pregnant women undergoing CS.

As regard heart rate we found statistically insignificant difference neither intraoperative nor postoperative between dexmedetomidine group and other two groups. Abdel Hamid et al., studied the effect of dexmedetomidine in sixty two patients which were randomly divided into two groups, Group (D) received 3.5 mL volume of 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 mL of preservative free normal saline intrathecally and Group (P) received 0.5 ml normal saline added to the same dose of heavy 0.5% bupivacaine and served as placebo for lower abdominal surgeries**.** They found that bradycardia (considered when heart rate <50 bpm) occurred in 8 cases in group D compared to none of the study patients in group P which is not consistent with our results [12].

Bradycardia in the dexmedetomidine group is believed to be due to postsynaptic activation of central alpha 2 adrenoceptors (α2-ARs) results in sympatholytic effect, leading to hypotension and bradycardia, an effect judiciously used to attenuate the stress response of surgery [13].

In agreement with our results, Shukla et al, that showed insignificant effect of dexmedetomidine and magnesium sulfate on heart rate when added to intrathecal bupivacaine [14].

As regard SBP, DBP and MAP intra-operatively and postoperatively when comparing dexmedetomidine with the two groups; there were no statistically significant differences ($P<0.05$) at all times of the study period. Hypotension considered only if there was decrease in SBP by more than 20% from base line. In agreement with our results, Kanazi et al Showed insignificant effect of dexmedetomidine on SBP when added to intrathecal bupivacaine [15]. Additionally, Al-Mustafa et al using 5μg, and 10 μg dexmedetomidine, found a dose dependent, but still insignificant, decrease in the SBP when compared to the bupivacaine (control) group [16].

Moreover, Sunil et al evaluated 90 patients and randomly allocated them to three groups of 30 each to receive intrathecally either 15 mg hyperbaric bupivacaine plus either 10 μg dexmedetomidine (group D), 25 μg fentanyl (group F) or 50 mg magnesium (group M). They found the (mean ± SD) MAP in the operation theater measured during 1st hour, showing no significant difference among the groups. Additionally, MAP values were comparable among three groups in PACU [17].

As regard SaO2 there were no significant differences between the three groups. In agreement with our results, Shukla et al, showed insignificant effect of dexmedetomidine and magnesium sulfate (Mg) on SaO2when added to intrathecal bupivacaine (the SpO2 was higher than 95% in all patients in the three groups, either in the intraoperative or in the PACU times) [14].

Regarding the side effects (backache and headache), there were no statistically significant different ($P>0.05$) between the different groups. This was in agreement with Magdy et al., who reported the addition of low-dose dexmedetomidine intrathecally (5μg) or intravenously (0.5 μg/kg/h) to spinal anesthesia for CS attenuates maternal hemodynamics and the hormonal response to CS without adverse effects (as nausea, vomiting, headache, and shivering) [18].

Also Sunil et al who found no neurological impairment related to spinal anesthesia such as back, buttock, leg pain, weakness, headache or any new neurological deficit. No patients suffered from respiratory depression or shivering during this study [17].

In conclusion, we found that low-dose of dexmedetomidine (5μg) intrathecally during CS has no significant adverse effects on the maternal hemodynamics when compared with magnesium sulphate.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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