



Magnesium Sulfate and Clonidine; Effects on Hemodynamic Factors and Depth of General Anesthesia in Cesarean Section

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Abstract

Background: Making stable hemodynamic and also durable unawareness is a daily challenge in the setting of general anesthesia in women who undergo surgical delivery of neonate and have limitations to receive opioids derivatives.

Objectives: We aimed to evaluate the effects of magnesium sulfate and clonidine on hemodynamic changes and depth of anesthesia and in mentioned mothers and also in neonatal APGAR index.

Methods: Current randomized, double-blind controlled trial study was conducted among a total of 360 pregnant females (38 - 41 weeks of gestation) who underwent elective cesarean section. Participants were randomly divided into three drug-receiving groups (equal 120 members): magnesium sulfate (30 mg/kg), clonidine (3 µg/kg), and placebo (0.9% NaCl). Patients' blood pressure, heart rate, cerebral state index (CSI) in specific time zones, and also late 24-hour recall were recorded. The CSI is an electroencephalographic monitoring method helping to assess the depth of anesthesia. Neonatal parameters, including APGAR score and umbilical venous blood sampling, were measured.

Results: Mean patients' age was 28 ± 4.5 . A significant decreasing and stabilizing effect of magnesium sulfate and clonidine on hemodynamic parameters (blood pressure and heart rate) was revealed ($P < 0.001$). Evidence implied on deeper anesthesia (lower CSI) among drug receivers comparing to placebo ($P < 0.001$). None of the participants experienced a late 24-hour recall postoperatively. All neonates were healthy, and no decrease was reported in APGAR score at minutes 1 and 5. Umbilical blood gas analysis showed no signs of acidosis and/or hypoxemia.

Conclusions: Adjuvant administration of either magnesium sulfate or clonidine is associated with hemodynamic stability and favorable unawareness in the setting of elective surgical delivery.

Keywords: Magnesium Sulfate, Clonidine, Cesarean Section, General Anesthesia, Blood Pressure, Hemodynamic

1. Background

Hemodynamic instability and awareness sequels are two major long-term morbid complications of poor general anesthesia, disturbing patients postoperatively, particularly in cardiovascular, trauma, and surgical delivery. By definition, a patient who recalls perioperative events postoperatively was aware due to an insufficient anesthetic approach (1). Unfortunately, awareness is a potential side effect to make debilitating psychosomatic outcomes (2). Anesthetic medications play a fundamental role in preventing awareness, recall, and unpleasant experience, and also would directly affect hemodynamic factors, including blood pressure and heart rate for surgical patients. In the

case of cesarean section, induction of general anesthesia begins with intravenous injection of hypnotic agents and neuromuscular relaxants and then followed by infusion of benzodiazepines and opioids, while delivery is accomplished and the umbilical cord is clamped. The latter is due to preventing adverse effects of benzodiazepines and opioids on the fetus, such as hypnosis, apnea, hypoxemia, acidosis, and APGAR score reduction. However, this preventive approach for the fetus is associated with poor anesthesia and a higher risk of awareness and hemodynamic instability for mothers (3). Contraindication of benzodiazepines and opioid usage and its accompaniment with increasing risk of awareness implied that applying alternative drugs to make satisfying anesthesia is recommended.

Clonidine is an imidazole with α_2 -agonist activity and analgesic effects, which also improves perioperative hemodynamic status, regulates sympathoadrenal responses, decreases the need for analgesic agents, and postoperative pain and discomfort (4). Magnesium sulfate activates an antagonist of the N-methyl-D-aspartate (NMDA) receptor that is a potent drug to prevent and relieve pain through depressing the central nervous system and peripheral neuromuscular transmission blockage at neuron end-plate (5).

2. Objectives

This study aimed to evaluate the effects of magnesium sulfate and clonidine on hemodynamic change and, concurrently, depth of anesthesia in women who underwent elective cesarean section and also to study probable neonatal APGAR changes regarding these two drugs.

3. Methods

This study was conducted from April 2017 to May 2019 as a double-blind, randomized clinical trial that was supervised under the department of anesthesia of medical college and also approved by the local committee of ethical rights with a registry code number of p/29/5/1/3159. The study received a registered code for clinical trial as IRCT2013021112425N1. Participants were mothers classified as class I by the definition of the American Society of Anesthesiologists (ASA-I) who were consecutively referred to a single general health care center and, finally, planned for elective surgical delivery. They participated in the study after signing written informed consent preoperatively. The participants were randomized systematically by a computer system to make three groups with equal 120 members. Regarding the double-blind method, both patients and medical caregivers, including a gynecologist (single common specialist for all operations) and assistants who registered data, were blind to the study. The patients with a documented or suspicious history of systemic arterial hypertension, diabetes mellitus, cardiovascular disease, kidney disease, neuromuscular disease, neuropsychiatric disorders, preeclampsia, allergy to magnesium sulfate or clonidine, consumption of neuroleptic or anticonvulsant drugs and all who underwent emergency cesarean section were excluded. The study required at least 120 patients to work valuably based on previous data statistical extractions. Totally, 360 pregnant women, whether with a previous history of childbirth or not, experienced an uncomplicated elective cesarean section were included.

The participants were stratified in three groups (magnesium sulfate, clonidine, and placebo) with equal 120 members. Thirty mg/kg of diluted magnesium sulfate 50% (Infu-Magnesol, Shahid Ghazi Pharmaceutical Co, Iran) in 100 cc of 0.9% saline fluid was slowly infused, Clonidine hydrochloride 100 $\mu\text{g}/\text{mL}$ (Clonidine Hydrochloride Injection, Cadila Healthcare Ltd, India) with a dose of 3 $\mu\text{g}/\text{kg}$ (equivalent to 200 μg) was given, and the placebo group underwent infusion of 100 cc of 0.9% NaCl solution, all intravenously and through 30 minutes at a time of induction and was not repeated afterward. Complete hemodynamic monitoring by using continuous pulse oximetry, electrocardiography, and non-invasive blood pressure and heart rate measurement was obtained for all by patient bedside monitoring (patient monitor, Alborz B5, Saadat Co, Iran). The cerebral state index (CSI) was evaluated by the attachment of CSI leads (DK-5000, Hersteller, Denmark) to frontal, temporal, and bilateral posterior auricular areas. The CSI is an electroencephalographic monitoring method applying for assessment of depth of anesthesia when a patient undergoes anesthesia in a general fashion. It measures brain signals (0:flat-100:awake state) and gives a score after analysis of signal characteristics. As a result, the lower the CSI score, the deeper the anesthesia experience. The mentioned variables were recorded precisely, just before and after the induction of anesthesia, immediately after tracheal intubation procedure, and at minutes 1 and 5 post-delivery of the fetus. Induction and maintaining of anesthesia were performed for all patients with a similar approach. After sufficient mask oxygenation, 5 mg/kg of sodium thiopental in combination with 1.5 mg/kg succinylcholine were injected intravenously, followed by tracheal intubation. In order to maintain anesthesia, inhaling 50% N_2O , 50% O_2 , and 0.6% isoflurane in association with intravenous infusion of 0.25 mg/kg atracurium besylate were applied. While the neonate was delivered and just after the umbilical cord was clamped, 2 $\mu\text{g}/\text{kg}$ fentanyl were infused intravenously. Reversing muscle relaxation was performed for all patients, administering proper dosage of atropine sulfate and/or neostigmine. For confirmation of successful delivery, the APGAR score was recorded for all neonates at zero and the 5th minutes of life. Umbilical cord sampling from the umbilical vein was also performed for all neonates to evaluate blood gas patterns and probable hypoxemia (pO_2), hypercapnia (pCO_2), and acidosis (pH). Considering the experience of awareness, patients were asked "do you remember anything from the time you got unconscious until you got aware again?" The positive answer on the first day after surgery was recorded as recall. Data were analyzed using SPSS software Inc. version 20. Central indexes as mean and

standard deviation (SD) for variables were calculated. In order to compare groups, the chi-square and Fisher-Exact test were performed, considering $P < 0.001$ as the level significance.

4. Results

No obvious difference was observed among the three groups regarding age ($P > 0.6$). All surgical deliveries were done by cesarean section and general anesthesia approach. All delivered neonates had normal APGAR scores (9-10/10) (9.5 ± 0.24) just after (minute 1) and at 5 minutes of birth. Data showed no abnormality in APGAR components for neonates, either for drug receivers or placebo mothers. Umbilical vein blood sampling analysis revealed that mean pH, pO₂, and pCO₂ were 7.34 ± 0.25 , 28 ± 5.7 mmHg, and 41.2 ± 5.1 mmHg, respectively, with no statistical differences between groups ($P > 0.05$). Considering SBP, either magnesium sulfate or clonidine recipient had more considering stability in every specific time zones, particularly during 5 minutes after delivery in comparison to whom received placebo ($P < 0.001$). Similar findings were extracted for both diastolic blood pressure and heart rate changes in three groups ($P < 0.001$). The effect of the mentioned drugs on hemodynamic parameters was equal with no superiority to each other ($P > 0.5$). Considering the cerebral status index (CSI) in three groups of study, data indicated that a significant deeper anesthetic effect after using either magnesium sulfate or clonidine was evident compared with the placebo group ($P < 0.001$). Nonetheless, there was no obvious difference between magnesium sulfate and clonidine to make general anesthesia deeper ($P > 0.05$). Table 1 shows the study findings of maternal and neonatal variables in detail.

Data emphasized no positive recall phenomenon in 24 hours after surgical procedure among entrants, neither in medication nor in placebo recipients.

5. Discussion

Restrictions when using some drugs, including opioids derivatives and benzodiazepines in pregnancy termination before clamping the umbilical cord, caused to search for alternative medical approaches to finally yield more comfortable surgical delivery with better hemodynamic and anesthetic indices intra- and postoperatively. In this regard, the current study investigated the effects of magnesium sulfate and clonidine. Although many studies have stated the positive effects of these drugs in other surgical procedures, data were limited in the case of cesarean

section under general anesthesia. For instance, Morris et al. (6) found that applying 3 $\mu\text{g}/\text{kg}$ of clonidine in vascular surgery led to need lower plasma concentration of propofol. Another study demonstrated that a combination of 4 $\mu\text{g}/\text{kg}$ of Clonidine with sedatives and analgesics would maintain sedation longer effectively and reduce the CSI (7, 8). The results of this study also were consistent with those mentioned above; i.e., prescribing magnesium sulfate and clonidine is associated with lower CSI and deeper anesthetic phase in surgical delivery. Previously, magnesium sulfate, with 30 mg/kg bolus dose and 10 mg/kg/h infusion, was found to decrease CSI and blood pressure before delivery (9). This finding was in line with ours. Furthermore, ad-junction of other drugs such as dexmedetomidine to bupivacaine has been proven to make better analgesia and sedation in case of cesarean section (10). Additionally, applying tramadol as opioid derivatives is advantageous in the case of epidural anesthesia for parturient while analgesia and average postoperative medication use for analgesia was considered (11). However, some other studies have specified that magnesium sulfate, although decreased the need for plasma concentration of some anesthetic drugs, did not affect the depth of anesthesia or awareness (12). This may be due to different methods, drug dosage, sample characteristics, and focus zone of studies. Hemodynamic changes, including systolic and diastolic blood pressure, mean arterial pressure, and also heart rate decrease in a specific time, especially during the first five minutes after delivery that is significant in this study. It was consistent with findings of other studies, clarifying that even oral clonidine consumption preoperatively would stabilize and decrease blood pressure and HR both before and after intubation time (13). Although other authors have explained that clonidine effects on systolic blood pressure were not obvious during surgery, it was significant in recovery time (7). Gousheh et al. (14) have stated the use of crystalloid solutions compared with colloid ones would stabilize blood pressure and heart rate after spinal anesthesia during cesarean section. This issue was more prominent when another author added glucose to the crystalloid solution (15). In contrast, another study has revealed that infusion of phenylephrine to prevent overt either hypotension or bradycardia was associated with better symptom (nausea and vomiting) control and also resulted in favorable neonatal blood gas outcomes (16). Although we used crystalloid for all participants, the latter finding showed that the effect of other parameters should be kept in mind. In addition to the above-mentioned findings, interestingly, there is also some evidence about the use of opioid derivatives, especially remifentanyl to control maternal hypertension -with no adverse effect on the fetus- before umbili-

Table 1. Maternal and Neonatal Findings of the Study^{a, b}

	Magnesium Sulfate (N = 120)	Clonidine (N = 120)	Placebo (N = 120)	P Value
Maternal				
Age, y	28.2 ± 4.6	27.5 ± 4.4	28.3 ± 4.6	0.6
Gestational age, wk	38.1 ± 0.9	38.5 ± 1.1	38.4 ± 0.8	0.4
Weight, kg	83.2 ± 10.2	82.5 ± 10.8	82.7 ± 11.3	0.7
Height, cm	159.3 ± 5.2	161.4 ± 4.8	160.6 ± 5.3	0.5
Heart rate (per minute)				< 0.001 ^b
After anesthesia induction	97 ± 6	97 ± 8	103 ± 12	
5 minutes after delivery	76 ± 4	75 ± 5	92 ± 7	< 0.001 ^b
SBP ^c , mmHg				
After anesthesia induction	132 ± 2.8	127 ± 3.7	131 ± 4.4	
5 minutes after delivery	123 ± 3.1	117 ± 2.4	132 ± 5.2	
DBP ^d , mmHg				< 0.001 ^b
After anesthesia induction	88 ± 2.1	84 ± 4.4	88 ± 1.5	
5 minutes after delivery	76 ± 1.6	71 ± 2.3	84 ± 1.9	
MAP ^e , mmHg				< 0.001 ^b
After anesthesia induction	98 ± 2.3	95 ± 2.4	101 ± 2.8	
5 minutes after delivery	91 ± 1.9	88 ± 1.7	97 ± 1.8	
CSF ^f (0 - 100)				< 0.001 ^b
After anesthesia induction	54 ± 2	57 ± 3	72 ± 3	
5 minutes after delivery	55 ± 2	51 ± 2	60 ± 1	
Neonatal				
APGAR, min				> 0.05
1st	10	10	10	
5th	10	10	10	
Umbilical venous sample				> 0.05
pH	7.34 ± 0.56	7.35 ± 0.53	7.34 ± 0.6	
pCO ₂ , mmHg	41.5 ± 6.2	40 ± 5.8	42 ± 5.4	
pO ₂ , mmHg	29.3 ± 4.8	27 ± 5.5	29.7 ± 6.2	

^aValues are expressed as mean ± SD.

^bSignificance value between placebo and non-placebo groups.

^cSystolic blood pressure.

^dDiastolic blood pressure.

^eMean arterial pressure.

^fCerebral state index.

cal clamping, while she is under general anesthesia for cesarean section (17). These controversies may be due to hormonal based metabolism changes in pregnancy, including hemodynamic imbalance, organ function disturbance, renal clearance, protein bonding, and chronic phase reactants, leading to major changes in case of molecular and drug half-life time, that would decompensate by somehow novel and complex medication effects. APGAR score, as a valuable scale for neonate health during the initial time of

birth, was influenced neither with magnesium sulfate nor with clonidine consumption. Umbilical blood gas analysis also demonstrated no unfavorable hypoxemic and/or acidotic changes among neonates. These were revealed no accusation for neonatal side effects for these drugs in this study, at least during the first minutes of life. We found no opposite records in comparison to ours in the latter issue. As a result, magnesium sulfate and clonidine would be recommended if the risk of neonatal complication is

regarded. The current study showed no negative effects on using magnesium sulfate and clonidine regarding recall. Similarly, other findings cleared that there is no difference between clonidine and placebo to prevent recall and awareness experience in delivery (12). Surprisingly, another study stated that the type of surgical procedure in the field of gynecology, including cesarean section, would not affect the incidence of recall in patients (18). However, another investigation demonstrated that recall and awareness are more probable in gynecologic surgeries except for delivery (19). As mentioned, previous data have controversial findings in case of recall. The expansion of ideas may be due to several other causes except for the type of surgery or drug prescription alone. Although the anesthesia team's expertise directly affects this issue during the induction and maintenance of anesthesia, personal characteristics of patient preoperatively, past medical history, previous disturbing experience about surgery, postoperative complication events, and different research methods would implicitly influence the findings. Thus, it is recommended to conduct further studies to elucidate these findings. Although data were achieved in a single health care center, which was a referral one and the sample size was more enough than was needed, we could emphasize the validity of data. Finally, further studies among mothers with other specific medical conditions and worsen ASA scores are preferably recommended by authors.

5.1. Conclusions

General anesthesia is a challenging procedure in pregnancy. Intravenous infusion of either magnesium sulfate or clonidine would stabilize hemodynamic parameters in combination with making general anesthesia deeper in the setting of surgical delivery with at least no further acute risk for neonates.

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Footnotes

Authors' Contribution: Mehdi Rajabi suggested the study design, performed critical revision, and manuscript approval. Mohammad-Reza Razavizade and Zohreh Tabasi suggested the study design, performed data collection and

manuscript approval. Maryam Hamidi-Shad performed data collection. Hossein Akbari performed data analysis and statistics interpretation. Abbas Hajian performed manuscript drafting and statistics interpretation.

Clinical Trial Registration Code: The clinical trial registration code was IRCT2013021112425N1.

Conflict of Interests: All authors declare they have no conflicts of interest.

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