Implications of amantadine sulfate usage on intraoperative hemodynamics in patients undergoing corrective surgeries for spine deformities: a randomized-controlled trial

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Background
Corrective spine s urg eries for scoliosis and/or kyphosis are a major challenge. This study was carried out to test whether preoperative intravenous administration of amantadine sulfate could affect the intraoperative hemodynamics in patients undergoing major spine corrective surgeries.

Patients and methods
This is a prospective, randomized double-blind clinical trial. Twenty adult patients were included in the study. Patients were randomized equally into two groups (10 patients each). Group A received an intravenous amantadine sulfate infusion of 200 mg in a 500 ml bottle. Group B (control group) received a ringer lactate intravenous infusion (placebo). Unlabeled bottles were given slowly 3 h before the surgery. Intraoperative hemodynamics systolic, diastolic, mean arterial blood pressure, and heart rate were recorded.

Results
The intraoperative mean arterial blood pressure was significantly lower in group A than group B at induction) 57.5 ± 7.94 vs. 64.9 ± 6.18, $P = 0.002$) and half an hour after induction) 51.8 ± 6.66 vs. 59.2 ± 6.37, $P = 0.001$). Also, the intraoperative mean heart rate was significantly lower in group A than group B at induction (88.5 ± 16.07 vs. 101.2 ± 19.89, $P = 0.032$), 3 h after induction (81.5 ± 10.33 vs. 90.8 ± 16.46, $P = 0.039$), and at the end of the operation (95.3 ± 7.93 vs. 103.6 ± 9.37, $P = 0.004$).

Conclusion
Preoperative administration of intravenous amantadine sulfate in corrective spine surgery has minimal effect on intraoperative hemodynamics in terms of the mean arterial blood pressure and heart rate.

Keywords:
amantadine sulfate, hemodynamics, spine surgery

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Introduction

The surgical procedure of spine deformities correction is usually lengthy, and involves large surgical exposure, long-standing nociceptive stimulation, and massive blood loss compared with other orthopedic interventions [1,2]. Also, instrumentation in surgery for spine deformities such as vertebral fusion, congenital, and traumatic scoliosis carries a risk of injury to the spinal cord during spinal surgery; these complications are generally a result of complex factors such as direct effects of compression on the spinal cord, distraction, and the effects of spinal ischemia [3,4]. The most common drugs in the treatment of acute postoperative pain are still opioids, but their use is limited by adverse effects. It has been shown that the coadministration of drugs such as NSAIDs and paracetamol or N-methyl-D-aspartate (NMDA) receptor antagonists can minimize side effects and enhance the analgesic action of opioid [5–9].

The objective of this study was to determine to what extent the preoperative use of amantadine can affect the intraoperative hemodynamics.

Patients and methods

Study design

This prospective, double-blinded, randomized placebo controlled clinical trial was conducted in the Orthopedics Surgery theater and postoperative ICU in Assiut University Hospitals in the period from August 2017 to April 2019 after IRB approval (17100191) from the Medical Ethics Committee, Faculty of Medicine, Assiut University. Written informed consent was obtained from all the patients participating in this study in the preoperative visit, where they were screened for suitability and interest. Clinical trial registration number is: NCT03178708

Participants

Inclusion criteria were as follows: patients aged between 18 and 40 years of both sexes, ASA physical status I–II,

and scheduled for elective spine deformity correction surgery (scoliosis and/or kyphosis), with BMI of less than 35 kg/m^2.

Exclusion criteria

Patients with significant central nervous system, respiratory, cardiac, hepatic, renal, or endocrine dysfunction and allergy to any of the study medications were excluded.

Randomization

Randomization was performed using computer-generated randomization numbers. Numbers were kept in a sealed envelope and opened only on the night of surgery by an anesthetist not involved in intraoperative or postoperative data collection. Medication labels (amantadine sulfate and lactated ringer) were removed by the same anesthetist who opened the envelopes and bottles were relabeled according to the patient name and the envelope number. Participants, the surgeon, and the anesthesia group, which is responsible for anesthesia induction and monitoring, data collection intraoperative, and postoperative care, were blinded to randomization until data processing.

Groups

Patients were allocated randomly into one of two groups (10 patients in each). Group A received a relabeled bottle of amantadine sulfate intravenous infusion 200 mg (500 ml). Group B received a relabeled bottle of ringer lactate intravenous infusion (500 ml). The study drug preparations were administered slowly intravenous 3 h before the surgery.

Anesthetic technique

All patients were premeditated by intravenous midazolam 2–5 mg 30 min before surgery. Induction of anesthesia was performed with propofol 2–3 mg/kg, lidocaine 1 mg/kg, fentanyl 2 μg/kg, and cis-atracurium 0.15–0.20 mg/kg. Anesthesia was maintained with an O^2/air mixture (50–50%), sevoflurane 1.5–3% MAC, regular maintenance doses of cis-atracurium, and mechanical ventilation with parameters adjusted according to body weight. Intraoperative monitoring included noninvasive blood pressure, end-tidal CO_2, $SpaO_2$, heart rate, and urine output.

The patient was placed in the prone position with an uncompressed abdomen. The peripheral nerves, eyes, genitals, and bony points were padded and protected. Intravenous fluids were warmed, and a warming mattress device was used. Ringer lactate and blood products were administered according to the amount of blood loss and the patient's weight. All patients received tranexamic acid 20 mg/kg intravenous after induction of anesthesia [10,11]. For intraoperative neurological monitoring, the wake-up test was used as it is the tool used for assessment in our institute. At the end of the surgical procedure, neuromuscular blockage was reversed with neostigmine 0.05 mg/kg and atropine (0.4 mg/1 mg neostigmine), and patients were extubated.

Evaluation periods

Patients' demographic and clinical data were recorded. The intraoperative assessment included vital signs (systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate), which were recorded before induction, at induction, half an hour after induction, and every hour to the end of the surgery.

Statistical analysis

Sample size calculation based on that for the purpose of this preliminary study, it was decided to recruit 20 patients. Based on an anticipated attrition rate of 15–20% due to complications, adverse effects, protocol violations and patient withdrawal, a total of 20 patients were recruited.

Data were analyzed using SPSS, version 20.0 software programs (IBM Corp., Armonk, NY, USA). The data were tested for normality using the Kolmogorov–Smirnov test and for homogeneity variances before further statistical analysis. Categorical variables were described as number and percent, whereas continuous variables were described as mean ± SD. The χ^2 test and the Fisher exact test used to compare categorical variables. Continuous variables were compared using an independent-samples *t* test. A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

In total, 20 patients were evaluated during the period from June 2017 to March 2019; 20 patients fulfilled the inclusion criteria and completed the study. There was no statistically significant difference between the study groups in demographic data (age, sex, weight, and height) (Table 1).

There were no statistically significant differences in operative time, the total amount of intraoperative fluid administered, and urine output between the two study groups (Table 1).

The systolic blood pressure was significantly lower in group A than group B at certain times of the operation: at induction (92.1 ± 11.96 vs. 105.9 ± 9.74, $P < 0.001$) half an hour after induction) 80.5 ± 8.36 vs. 96.7 ± 10.63, $P < 0.001$), and 3 h after induction (85.2 ± 10.31 vs. 93.5 ± 14.7, $P = 0.046$) (Fig. 1).

On comparing the diastolic blood pressure between two groups, it was found to be significantly lower in group A than group B half an hour after induction (40.4 ± 6.76 vs. 48.7 ± 8.6, $P = 0.002$) and 3 h after induction (43.8 ± 7.02 vs. 50.5 ± 9.3, $P = 0.014$) (Fig. 2).

There was a statistically significant difference in the intraoperative mean arterial blood pressure; it was significantly lower in group A than group B at induction) 57.5 ± 7.94 vs. 64.9 ± 6.18, $P = 0.002$) and half an hour after induction) 51.8 ± 6.66 vs. 59.2 ± 6.37, $P = 0.001$) (Fig. 3).

Also, the intraoperative mean heart rate was significantly lower in group A than group B at induction (88.5 ± 16.07 vs. 101.2 ± 19.89, $P = 0.032$, 3 h after induction (81.5 ± 10.33 vs. 90.8 ± 16.46, $P = 0.039$), and at the end of the operation (95.3 ± 7.93 vs. 103.6 ± 9.37, $P = 0.004$) (Fig. 4).

Table 1 Demographic and surgical data

	Group A (mean±SD)	Group B (mean±SD)	*P*
Sex [*n* ()]			
Male	3 (30)	4 (40)	1.000
Female	7 (70)	6 (60)	
Weight	46±7.54	48.5±7.27	0.293
Height	147±5.71	150.2±5.5	0.079
Age	18.5±0.76	19.4±2.26	0.099
Operative time (min)	357±113.88	324±72.58	0.281
Fluid (ml)	2845±1159.16	2750±638.67	0.750
Urine output (ml)	410±160.26	375±80.3	0.388

Discussion

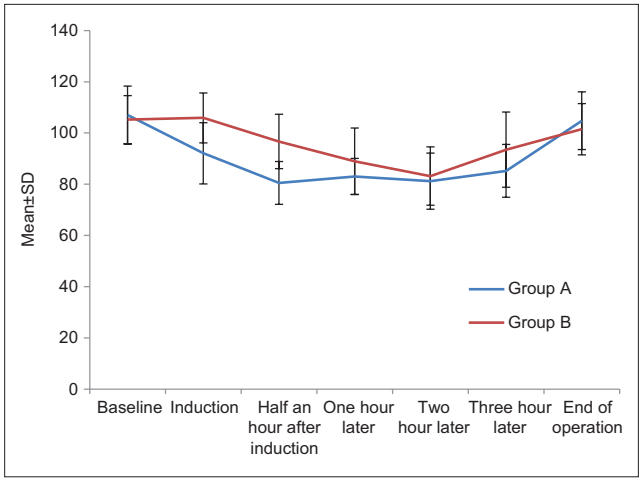
This study was carried out in Assiut University Hospital, Orthopedics Surgery theater, and postoperative ICU to determine the effect of preoperative administration of intravenous amantadine sulfate on the intraoperative hemodynamics in patients undergoing corrective surgery for spine deformities.

Many drugs have been used as an additive to the anesthetic plan to decrease the total amount of opioid consumption to decrease the incidence of side effects of opioids, some of these drugs that may attenuate analgesic action of opioids and potentiate the development of tolerance are NMDA receptor antagonists [5,7,12]. Many trials have used different types of NMDA receptor antagonists as coanalgesics postoperatively [12,13].

Amantadine is one of the NMDA antagonists and is used in the treatment of viral infection such as influenza type A and is also commonly used in the treatment of Parkinson's disease. Amantadine at lower concentrations acts predominantly as an NMDA receptor antagonist, whereas at higher concentrations, it can interact with other types of receptors and may also influence the release of dopamine from the presynaptic bulb [14–16].

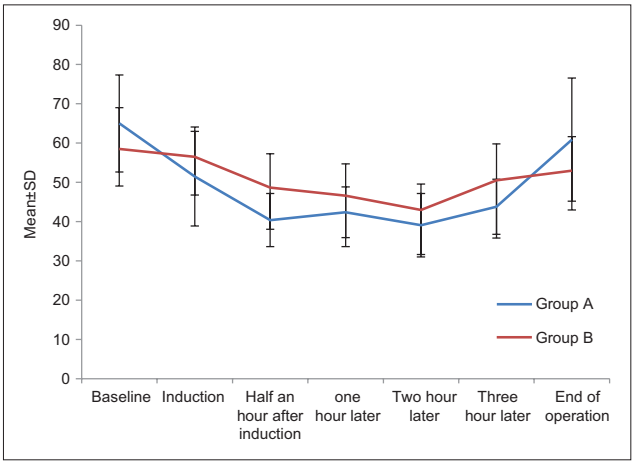
The main findings of our study are that the mean intraoperative arterial blood pressure was significantly lower in group A (amantadine group) than group B (placebo group) at induction and half an hour after induction. Also, the intraoperative mean heart rate was significantly lower in group A than group B at

Figure 1



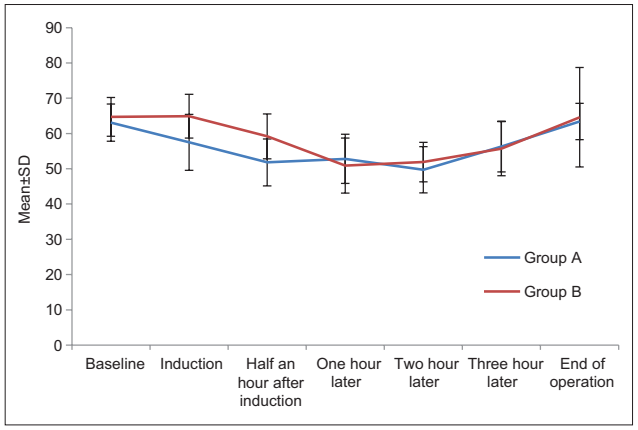
Systolic blood pressure in the study groups.

Figure 2



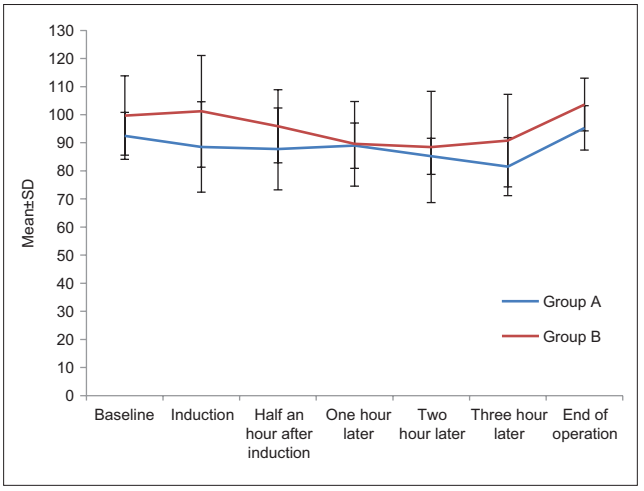
Diastolic blood pressure in the study groups.

Figure 3



Mean arterial blood pressure in the study groups.

Figure 4



Heart rate in the study groups.

induction, three hours after induction, and at the end of the operation.

The explanation for the changes in the intraoperative hemodynamics is unclear and this may be because the NMDA receptor plays an important role in the process of central sensitization. Excitatory amino acids, such as glutamate and aspartate, activate the NMDA receptor, leading to an increase in intracellular calcium and activation of second messengers, which stimulate protein kinases and modify neuronal excitability. NMDA receptor activation may also produce longer-lasting changes by stimulating new gene expression. The role of the NMDA receptor in the development of central sensitization, acute opioid tolerance, and opioid-induced hyperalgesia has led to renewed interest in NMDA receptor antagonists for clinical use in humans [9,17,18] and one of these substances is amantadine. Therefore, amantadine may be useful in decreasing pain and analgesic requirements, possibly by preventing postsurgical central sensitization, acute opioid tolerance, and opioid-induced hyperalgesia, which will be presented by more stability in intraoperative hemodynamics and decrease intraoperative opioid requirements.

Limitations of the study

(1) The dose of amantadine used is low and has relatively decreased potency of amantadine in NMDA receptor blocking.
(2) The number of patients enrolled in this study was too small to evaluate the effect of amantadine sulfate.

Conclusion

Preoperative administration of intravenous amantadine sulfate in corrective spine surgery has minimal effect on intraoperative hemodynamics in terms of the mean arterial blood pressure and heart rate.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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