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Research Article

Effect of preoperative oral amantadine on intraoperative anesthetic and analgesic requirements in female patients during abdominoplasty

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KEYWORDS

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Abstract *Background:* We hypothesized that NMDA antagonist, amantadine, may be beneficial in reducing the intraoperative anesthetic and analgesic requirements. The aim of this study to evaluate the effect of preoperative oral amantadine on induction doses of propofol, intraoperative anesthetic and analgesic requirements.

Methods: In a prospective, randomized, double-blinded controlled study 60 female patients ASA I or II aged 18–60 years old, planned for abdominoplasty surgery divided into two groups (30 patients each). Group A: received oral amantadine 200 mg on the evening before surgery and 200 mg 60 min prior to surgery. Group P (control group): the patients received placebo capsules. Propofol and isoflurane were titrated guided by BIS during induction and maintenance of anesthesia where the total dose of propofol and the time elapsed between injection of propofol to achieve BIS value 60 were recorded. Also, the inspired isoflurane concentrations required to maintain BIS between 40 and 60 and the total dose of fentanyl needed to maintain adequate analgesia were recorded.

Results: The induction dose of propofol and the time from propofol injection till BIS value reached 60, the total intraoperative fentanyl requirements and the inspired isoflurane concentration required to maintain BIS reading between 40 and 60 were statistically significant lower in amantadine group compared to placebo treated group. The two groups were similar regarding the occurrence of side effects.

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Conclusion: Preoperative oral amantadine reduced the induction time, induction dose of propofol, intraoperative anesthetic and analgesic requirements compared to placebo without serious side effects in female patients during abdominoplasty.

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1. Introduction

The N-methyl-d-aspartate (NMDA) receptor activation by excitatory neurotransmitters as aspartate or glutamate increase in intracellular calcium with activation of second messengers that modify neuronal excitability with development of central sensitization of the dorsal horn neurons in response to noxious stimulus [1].

The NMDA receptor antagonists have been shown to potentiate the potency of volatile anesthetics in animal study [2] and useful in prevention of central sensitization, and opioid-induced hyperalgesia leading to decrease of the postoperative pain and analgesic consumption [3].

Amantadine (1-aminoadamantane), a non-competitive NMDA antagonist, was used for long time for treatment of Parkinsonism and as an antiviral against influenza. It has been found that perioperative oral amantadine reduced postoperative pain and analgesic requirements [1].

To our knowledge there were no reports evaluating the effect of amantadine on intraoperative anesthetic and analgesic requirements, therefore we hypothesized that the amantadine as a NMDA antagonist might be beneficial in reducing the intraoperative anesthetic and analgesic requirements. This study was designed in a prospective, randomized, double-blinded controlled manner to evaluate the effect of preoperative oral amantadine 200 mg on the evening before surgery and 200 mg capsule 60 min prior to surgery on induction doses of propofol, intraoperative anesthetic requirements guided by BIS and intraoperative analgesic requirements.

1.1. Methods

After approval of the local ethical committee, a written informed consent obtained from 60 female patients American Society of Anesthesiology (ASA) physical status I or II aged 18–60 years old, planned for abdominoplasty under general anesthesia in Dar Alshifa hospital (State of Kuwait) from January 2010 to January 2011.

Patients with ASA class more than II were excluded from the study; patients with history of allergy to amantadine or ingestion of dextromethorphan (cough suppressant) within 48 h before surgery were also excluded.

In the preoperative visit, the patients were informed about the study protocol.

Patients were randomly divided to two equally divided groups (30 patients each) by using the closed envelop technique. To maintain the blind nature of the study, the studied drugs were prepared by an anesthesia nurse according to the instructions written in a sealed envelope and were given to the patients by the ward nurses as follows:

- Amantadine group (group A): the patients received oral amantadine using the dose used in the study of

Snijdelaar et al. 200 mg capsule on the evening before surgery and 200 mg capsule 60 min prior to surgery (Symmetrel, Novartis pharma AG., Basel, Switzerland).

- Placebo group (group P) (control group): the patients received placebo capsules.

No sedative premedication were given to the patients. When the patients reached the operation room, an 18 gauge intravenous cannula was inserted and the monitors including ECG, pulse oximetry, non-invasive blood pressure, and skin temperature were attached. The depth of anesthesia was monitored using the Bispectral index (BIS) monitoring, where the BIS electrodes were placed on the forehead and were connected to the BIS monitoring system (Aspect Medical Systems, Leiden, The Netherlands).

In this study, both propofol and isoflurane were titrated guided by BIS in a standardized technique to evaluate the effect of amantadine premedication on intraoperative anesthetic requirements.

General anesthesia was induced using fentanyl $1 \mu\text{g kg}^{-1}$ and propofol titration using the regimen used by Turkistani et al. [4] where propofol was administered in 10 mg boluses over 5 s every 15 s till the BIS value reached 60 where the time taken to reach this value was recorded and the total dose of propofol required to achieve this value was recorded. Cisatracurium 0.15 mg kg^{-1} was given and the trachea was intubated with oral cuffed tube lubricated with lidocaine jell 2% 2 min after cisatracurium administration; controlled ventilation was adjusted to maintain end-tidal CO_2 35–40 mmHg. Anesthesia was maintained with isoflurane 1.2% in 50% $\text{N}_2\text{O}/\text{O}_2$ mixture with adjustment of the isoflurane to maintain BIS value between 40 and 60 in order to maintain adequate depth of anesthesia. Analgesia was maintained by fentanyl 50 μg when signs of inadequate analgesia (> 20% increase in the heart rate and mean arterial blood pressure from the baseline) were observed. Muscle relaxation was maintained with cisatracurium boluses in response to peripheral nerve stimulator.

At the end of surgery, isoflurane and N_2O were discontinued and muscle relaxant was reversed by atropine and neostigmine. Following extubation, patients were transferred to the recovery room where patients were monitored until they fulfilled the criteria of the modified Alderate scores.

The following were evaluated by an anesthesiologist unaware of the studied groups:

- (1) Demographic data and duration of surgery.
- (2) Induction dose of propofol.
- (3) Time from propofol injection till BIS value reached 60 (T1).
- (4) The inspired isoflurane concentrations at BIS value 40–60 were collected every 10 min and the mean isoflurane concentration during the procedure were recorded.

- (5) The total dose of intraoperative fentanyl needed to maintain adequate analgesia.
- (6) Time for BIS value to reach 80 following isoflurane discontinuation (T2).
- (7) Postoperative side effects such as.
 - Nausea and vomiting (treated with ondansetron 4–8 mg i.v.).
 - Sedation (*graded on a five-point scale: 1: fully awake and oriented; 2: drowsy; 3: eyes closed, arousable to command; 4: eyes closed, arousable to physical stimulation; and 5: eyes closed, unrousable to physical stimulation*) [5].
 - Respiratory depression.

1.2. Statistical analysis

The sample size in this study was calculated similar to that in the study of Turkistani et al. taking the propofol dose required to decrease the BIS to below 60 as the primary outcome with the power was set at 85% and the α -error level was fixed at 0.05. Data values were presented as means (SD) or number (percentages). Numerical data were analyzed by using Student's unpaired *t*-test. Nonparametric data were analyzed by using the Mann Whitney *U*-test. A value of $P < 0.05$ was considered significant. All statistical analysis was performed using (Microsoft Excel 2003).

2. Results

There were no significant differences between the two studied groups regarding age, sex, ASA state and duration of surgery (Table 1).

During induction, the induction dose of propofol and the time from propofol injection till BIS value reached 60 was statistically significant lower in amantadine group compared to placebo treated group ($p < 0.05$) without significant difference between the two groups in the time for BIS value to reach 80 following isoflurane discontinuation (Table 2).

During maintenance of anesthesia, total intraoperative fentanyl requirements and inspired isoflurane concentration required to maintain BIS reading between 40 and 60 were statistically significant lower in amantadine group compared to placebo treated group ($p < 0.05$) (Table 3).

There were no significant differences between the two studied groups regarding perioperative heart rate and mean arterial blood pressure at different time of measurements (Figs. 1 and 2).

Nausea developed in four patients in amantadine group and five patients in placebo treated group without statistically significant difference between two groups, with development of vomiting in one patient of the amantadine group without occurrence of sedation or respiratory depression in the two studied groups (Table 4).

3. Discussion

This study demonstrates that oral premedication with amantadine 200 mg on the evening of surgery and 200 mg 60 min prior to surgery reduced the induction time and dose of propofol and intraoperative isoflurane consumption required to reduce the

Table 1 Patient characteristics and operative data.

	Group (P) (n = 30)	Group (A) (n = 30)
Age (years)	47(4)	48(4)
Weigh (kg)	86(4.2)	82(3.4)
ASA physical status (I/II)	19/11	20/10
Operation time (min)	106(8)	103(9)

Group P: Placebo group, Group A: amantadine group. Data presented as mean (SD), number.

No significant differences between the studied groups.

Table 2 Time from propofol injection till BIS value reached 60 and Time for BIS value to reach 80 following isoflurane discontinuation.

	Group (P) (n = 30)	Group (A) (n = 30)
T1 (sec)	97(1.4)	86(1.3)*
T2 (min)	5.3(0.4)	5.7(0.6)

Group P: Placebo group, Group A: amantadine group. Data presented as mean (SD). T1: time from propofol injection till BIS value reached 60, T2: time for BIS value to reach 80 following isoflurane discontinuation.

* Significant difference compared to group P ($p < 0.05$).

BIS reading to 40–60 compared to placebo treated patients. This is consistent with the finding of the animal study of Daniell who reported that NMDA antagonists potentiate the general anesthetics [2].

In this study, BIS monitoring was used because it can be considered a useful method of detecting inadequate sedation, analgesia, or both during general anesthesia [6].

To our knowledge few studies are available evaluating the analgesic effect of amantadine, therefore; we used reports of other NMDA antagonists to compare our findings.

The ability of NMDA antagonists to reduce pain is controversial, some reports were inconsistent with our findings; the study of Snijdelaar and colleagues reported that perioperative oral amantadine 200 mg on the evening before surgery; 200 mg at 1 h before surgery; and 100 mg at 8, 20, and 32 h after surgery decreased postoperative pain and morphine requirements after radical prostatectomy [1]. Kawamata et al. [7] found that preoperative oral dextromethorphan decreased pain and analgesic consumption after tonsillectomy in adults, Abu-Samara and Ismaeil [8] found that oral dextromethorphan administered 90 min before surgery decreased postoperative pain after functional endoscopic sinus surgery. Heidari et al. [9]

Table 3 Doses of propofol, fentanyl and Isoflurane.

	Group (P) (n = 30)	Group (A) (n = 30)
Induction dose of propofol (mg)	168(13.4)	126(9.6)*
Total intraoperative fentanyl (μ g)	133.8(6.9)	83.8(7.3)*
Inspired isoflurane concentration (%)	1.7(0.07)	1.1(0.08)*

Group P: Placebo group, Group A: amantadine group. Data presented as mean (SD).

* Significant difference compared to group P ($p < 0.05$).

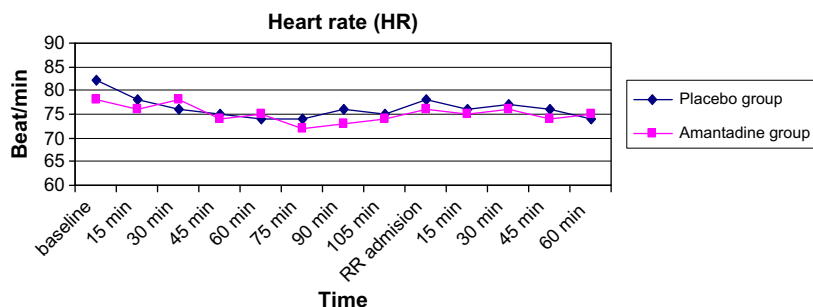


Figure 1 Perioperative heart rate (HR) in the two studied groups, No significant differences between the studied groups.

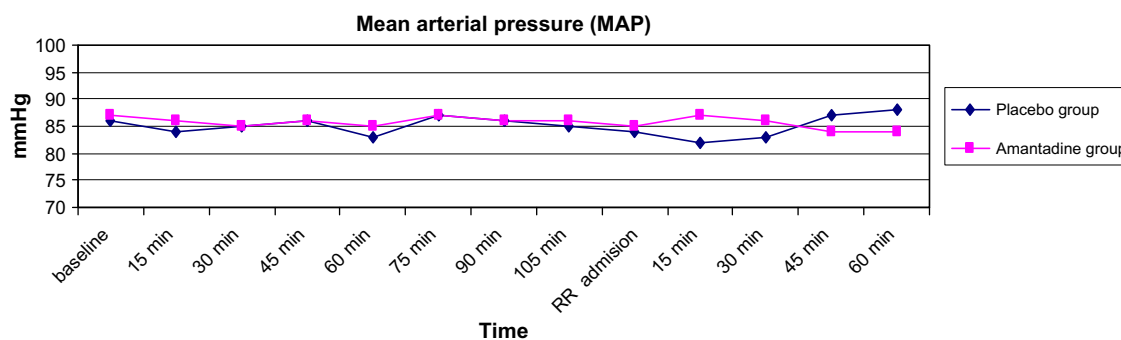


Figure 2 Perioperative mean arterial blood pressure (MAP) in the two studied groups, No significant differences between the studied groups.

found that oral ketamine was effective in reducing postoperative pain and analgesic requirements after orthopedic surgery. In addition Seyhan et al. [10] concluded that i.v. magnesium sulfate reduced intraoperative anesthetic and postoperative analgesic requirements. Also, Ryu and colleagues [11] reported that i.v. magnesium sulfate reduced postoperative analgesic consumption.

The mechanism by which NMDA antagonists may reduce pain and opioid consumption, by preventing the development of central sensitization to noxious stimulus and reducing opioid tolerance in many animal and human studies [3].

Contrary to the previous studies; Gottschalk et al. [12] reported that preoperative intravenous 200 mg of amantadine given 30 min before surgery did not reduce the postoperative opioid requirements in women undergoing abdominal hysterectomy, this may be due to the difference in the amantadine dose and route (two oral doses in our study and single intravenous dose in Gottschalk et al. study) and the type of surgery being extra abdominal surgery in our study, Rose et al. [13] concluded that preoperative oral dextromethorphan 1 h before surgery has no opioid sparing effect in children after adenotonsillectomy and Mahmoodzadeh et al. [14] found that oral dextromethorphan administered two hours before surgery, did not decrease postoperative pain intensity and morphine requirement after cholecystectomy.

Further studies are required to study the effect of different doses of amantadine on intraoperative anesthetic requirements.

We concluded that preoperative oral amantadine 200 mg on the evening of surgery and 200 mg 60 min before surgery reduced the induction time, induction dose of propofol, intraop-

Table 4 Postoperative side effects.

	Group (P) (n = 30)	Group (A) (n = 30)
Nausea	5(16%)	4(13%)
Vomiting	0(0)	1(3%)
Sedation	0(0)	0(0)
Respiratory depression	0(0)	0(0)

Group P: Placebo group, Group A: amantadine group. Data presented as number (percentage).

No significant differences between the studied groups.

erative anesthetic and analgesic requirements compared to placebo in female patients during abdominoplasty surgery.

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