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Original article

Effect of Magnesium Sulfate on Epinephrine-Mediated Adverse Effects during Liposuction Procedures: A prospective Randomized controlled Study

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ABSTRACT

Background: During liposuction procedures, injection of wetting solution containing epinephrine is performed. This may increase the risk of cardiovascular side effects in large volume cases. Magnesium sulfate has cardioprotective effects, and can prevent complications related to epinephrine.

The aim of the work: To assess the effect of adding intravenous magnesium sulfate, during the administration of epinephrine containing wetting solution, on the incidence of epinephrine-mediated cardiovascular side effects during liposuction surgery.

Patients and Methods: This was a prospective randomized study comprised a total of 94 cases into two equal groups. The epinephrine group included 47 cases that had epinephrine in their wetting solution, and epinephrine-Mg group included the remaining cases that had adrenaline in the wetting solution along with intra venous. administration of $MgSO_4$. Heart rate, blood pressure, arrhythmia incidence, isoflurane, and morphine consumption were recorded.

Results: No significant difference was noticed as regard basal and induction heart rate and mean arterial pressure [MAP]. However, the epinephrine-Mg group showed significantly lower readings on subsequent assessment. There was no significant difference among both groups regarding the incidence of arrhythmia; the epinephrine group had more cases with arrhythmia. Isoflurane consumption decreased significantly in the epinephrine-Mg group in comparison with the epinephrine group, while morphine consumption did not significantly differ between them.

Conclusion: Based on our findings, intravenous administration of magnesium sulfate decreases heart rate, blood pressure, and inhalational anesthesia consumption during liposuction. However, it has no significant impact neither on the incidence of arrhythmia, nor morphine consumption.

Keywords: Epinephrine; Magnesium Sulfate; Liposuction; Arrhythmia; Norepinephrine.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Liposuction is a common surgical procedures conducted by plastic surgeons. With surgical evolution, several modifications have been done to the original dry liposuction procedure, making surgery easier along with achieving better cosmetic results [1].

The advent of wetting solution which is injected into the subcutaneous tissue layer, helped to decrease bleeding reported in the early technique [2].

Furthermore, the liposuction procedures have become safer with the progress of wetting approaches; from the “wet technique,” to the tumescent and super wet techniques [2–4].

In routine practice, epinephrine 1:1000 [1mg/ml] is usually added to the wetting solution because of its vasoconstrictive effect. This leads to decreased bloody content in the aspirate, and prolonged duration of local anesthetic action [5]. Also, epinephrine mediated vasoconstriction prevents more absorption of that drug leading to a decrease in adrenergic side effects [6]. However, to improve surgical outcomes, the volume of wetting solution has been increased, and it was reported to reach up to 5 - 10 mg in large volume cases [7]. This may lead to increased incidence of epinephrine-induced side effects. Different studies have attributed mortality during liposuction surgeries to cardiac arrhythmias, myocardial infarction [MI], fatal asystole, pulmonary overload, and pulmonary edema [PE] [8, 9].

Although the clear cause of these complications is not well defined, epinephrine toxicity was demonstrated to have an essential role. The difficulty behind that may be due to short half-life of epinephrine, postmortem metabolism, and inability to differentiate between exogenous and endogenous epinephrine [10].

Magnesium is known to be beneficial for the cardiovascular health because of its ability to maintain membrane potential, magnesium also, blocks the release of catecholamines from both adrenergic nerve terminals and the adrenal gland, and moreover intravensous [IV] magnesium sulfate suppresses catecholamines discharge accompanied by tracheal intubation. Lastly, magnesium deficiency has been concerned in several cardiovascular pathologies including cardiomyopathy, hypertension, dyslipidemia, and atherosclerosis [11]. However, more studies need to be conducted to further explain the role of magnesium sulfate [$MgSO_4$] as a therapeutic agent to prevent or reverse certain of the above-mentioned cardiovascular situations [11].

AIM OF THE WORK

The hypothesis of the this study was administration of intravenous $MgSO_4$, during the infusion of the epinephrine containing wetting solution, would ameliorate the incidence of adrenaline mediated cardiovascular side effects during liposuction surgery. The primary outcome of the current study was the incidence intraoperative hemodynamic changes. Secondary outcomes were: inhalational anesthetics consumption in addition to postoperative analgesic effects.

PATIENTS AND METHODS

This was a prospective randomized controlled study conducted at Mansoura University Hospitals within the period from September 2019 to January 2021. We included a total of 94 cases prepared for liposuction. An informed written consent was obtained from all cases after complete explanation of the advantages and drawbacks of the injection technique. Also, the study was approved by the local ethical committee of Mansoura University by number R.20.09.1018.

Inclusion criteria: cases between 20 and 60 years, from either gender.

Exclusion criteria: cases whose age beyond the previous limit, ASA > 2, allergy to MgSO4, heart block, hypertension, diabetes mellitus, cardiovascular, renal diseases, endocrine e.g. pheochromocytoma, thyrotoxicosis, and metabolic diseases.

The cases were divided into two groups:

- The epinephrine group: included 47 cases that had epinephrine only in their wetting solution
- Epinephrine-Mg group: included the other 47 cases that had adrenaline in the wetting solution

along with i.v. administration of magnesium sulfate. Received 1 gm of $MgSO_4$ intravenously in 100 ml of isotonic saline over 10 min immediately as the same wetting solution was injected.

All cases are subjected to

- Preoperative preparation: 4 hours fasting, intravenous cannula insertion, ECG monitoring, blood pressure measurement, temperature and pulse oximetry usage. Pre-oxygenation with 100% oxygen had been carried for 2-3 minutes
- General anesthesia via propofol [0.5–2 mg/kg], fentanyl [1–2 μg/kg]. Tracheal intubation following a dosage of atracurium [0.05 mg/kg] and Volume-controlled ventilation was applied with FiO2 of 50% of 0.6–1.0 liter flow [low flow 0.6 to one LO2 50% + AIR50% +Isoflurane].
- After anesthesia and skin sterilization and injection of the wetting fluid was done. In the epinephrine group, 1 ml 1/1000 epinephrine was added to every 1000 ml of normal saline with total amount of 4 liters for case with average [0.04 mg/kg] epinephrine. In the epinephrine-Mg, 1 gm of $MgSO_4$ was intravenously administered in 100 ml of isotonic saline over 10 min immediately as the same wetting solution was injected.

During surgery, systolic blood pressure was maintained at baseline [80‐90 mmHg in normal patients]. Increase systolic blood pressure 20 % above normal was managed via firstly increasing depth of anaesthesia by increasing the dose of volatile anesthetics by 10% MAC. After 5 min if not controlled we increase the dose of volatile anesthetics by another 10% MAC. If heart rate was still, above 80 beat/min a 1mg propranolol was used, a second dose may be given after 2 min if heart rate not yet controlled. mean arterial blood pressure fallen below 50 mmHg, first we intervene through reduction depth of anaesthesia MAC by 10% .after 5 min if not getting desired response 5 mg of ephedrine was administered as incremental intra venous boluses to max 20 mg. in case of bradycardia [H R ‹ 50/ min] I V bolus of 0.5 mg atropine was given.

Restricted fluid therapy was adopted by; maintenance fluids [approximately 500ml normal saline .9%] administered throughout the operation, and additional intra-operative replacement fluids were corrected. with only 250mL crystalloid fluid was prescribed postoperatively in the recovery room. All patients resumed oral intake after about 4 hours stay in the recovery room under monitored anesthesia care and then were transferred to the ward. The patients had approximately 1250mL of crystalloid fluid with antibiotic on the floor for 24 hours [11]. Reversal of muscle relaxation with 0.04 mg/kg neostigmine and 0.02 mg/ kg atropine. Regaining consciousness, spontaneous breathing, and response to verbal command were extubation criteria.

- Continuous monitoring of MAP and heart rate, ECG, isoflurane consumption was measured using the next calculation [12]:

$$Fluid\ volatile\ agent = mean\ FGF\ [ml/\text{min}] \cdot mean\ agent\ conc.\ [Vol\%] \cdot Anaesth.\ duration\ [\text{min}]\ /\ Saturaded\ gas\ volume\ [ml] \cdot 100\ [Vol\ \%] = ml$$

- Acetaminophen 15 mg/kg was infused at the termination of surgery and repeated every six hours in the first postoperative day. The post-operative pain was reported using VAS immediately, 1, 4, 8, 12, and 24 h post-operatively. In cases which had VAS ≥4, 0.04 mg/kg i.v. morphine was given [13]. The total morphine consumption during the first post-operative day was recorded.

Statistical Analysis: Sample size was measured using the Power Analysis and Sample Size software [PASS] version 15.0.5 for windows [2017] using data obtained from a pilot study carried out on 12 cases in each limb of study groups [14] at Mansoura university hospital with heart rate at 15 min after subcutaneous injection of Saline-Epinephrine solution during liposuction as the primary outcome. Cases were allocated into two groups: The Mg Group and control Group. Heart rate at 15 min was 100.33 ± 4.31 for the Mg group and 104.67 ± 6.37 for the control group. A sample size of 42 cases in each group is needed to achieve a 95% power [1-β or the probability of rejecting the null hypothesis when it is false] in the suggested study using two-sided two-sample unequal-variance t-test with a significance level [α or the probability of rejecting the null hypothesis when it is true] of 5%. 10% drop-out is expected, so 47 cases will be included to each group.

RESULTS

Of the 101 patients evaluated for eligibility, 94 were assigned to one of the two groups. The remaining 7 were excluded [7 met exclusion criteria] [Figure 1]. With regard to demographic data, the mean age of the included cases was 35.32 and 37.19 years in groups, respectively. BMI values were 43.37 and 41.71 kg/m^2 in the study groups, respectively [p = 0.064]. ASA I score was present in 25.5 and 38.3% of cases in the study groups, respectively, whereas the remaining cases had ASA II score [p = 0.184] [Table 1].

Regarding HR, there was no significant difference among the two groups in terms of basal and induction heart rates [p = 0.239 and 0.332, respectively]. However, starting from wetting until 120 min during operation, the epinephrine-Mg group showed significantly lower heart rates compared to the epinephrine group [p < 0.05] [As shown in figure 2]. Similarly, mean arterial blood pressure showed the pattern expressed in the heart rate. There was no significant difference between the two study groups as regard both basal and induction readings [p = 0.778 and 0.295, respectively]. On subsequent readings, the epinephrine-Mg group showed significantly lower mean pressures in comparison with the epinephrine group [p < 0.05] [As shown in figure 3].

Although there was no significant difference among both study groups regarding the incidence of arrhythmia [p = 0.077], the epinephrine group had more cases with sinus tachycardia and premature ventricular contractions compared to the other group [Table 2]. Isoflurane consumption decreased significantly in the epinephrine-Mg group compare to the epinephrine group [83.83 vs. 97.87 ml, respectively, p = 0.002]. Although morphine consumption was less in the epinephrine-Mg group in comparison with the other group, there was no significant difference among the two groups [Table 3].

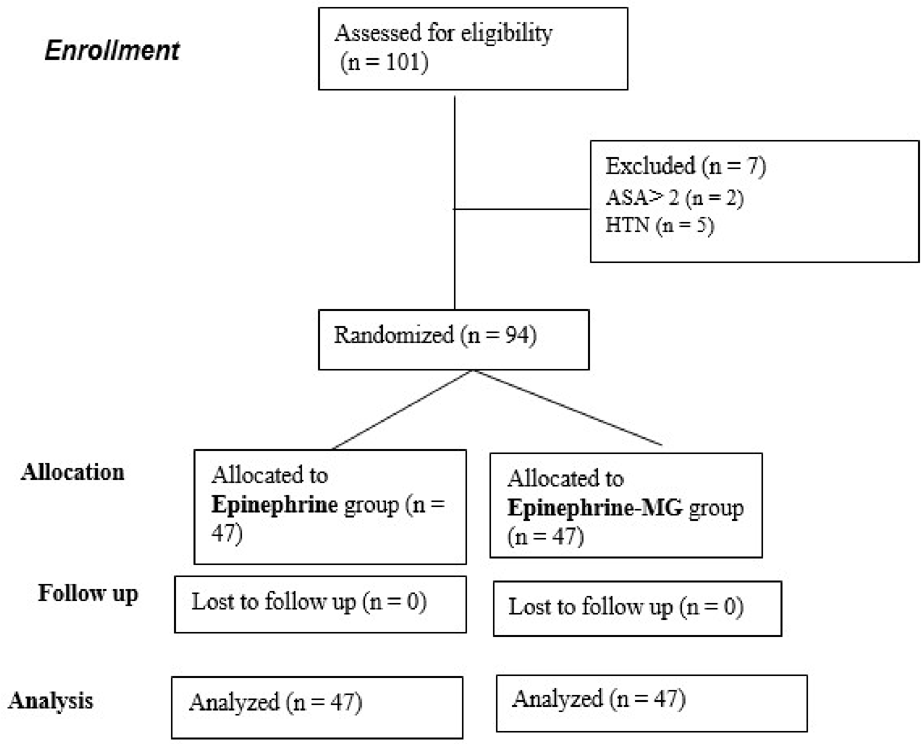

Figure [1]: Consort chart follow up

Table [1]: Demographic data in the groups being studied.

Variables		**Epinephrine group**	**Epinephrine-Mg group**	**P value**
Age [years]		35.32 ± 8.346	37.19 ± 9.925	0.325
Gender	**Male**	38.3% [18]	23.4% [11]	0.118
	Female	61.7% [29]	76.6% [36]	
BMI [kg/m²]		43.37 ± 4.452	41.71 ± 4.159	0.064
ASA	**I**	25.5% [12]	38.3% [18]	0.184
	II	74.5% [35]	61.7% [29]	

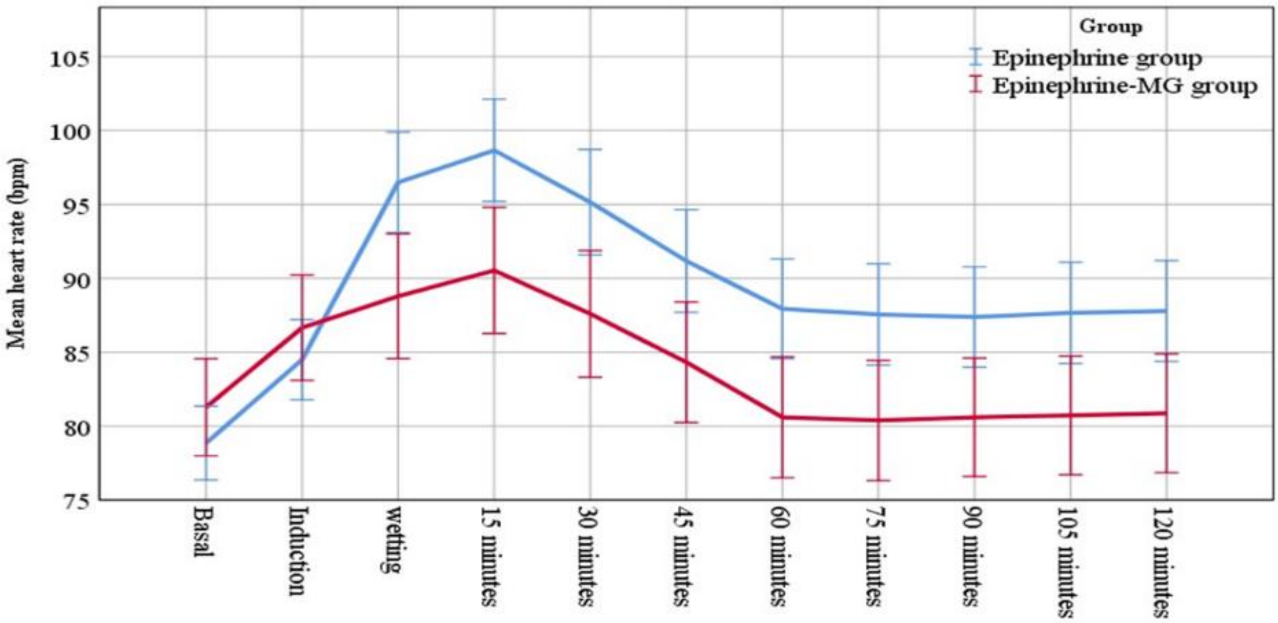

Figure [2]: Basal and intra-operative heart rates the study groups.

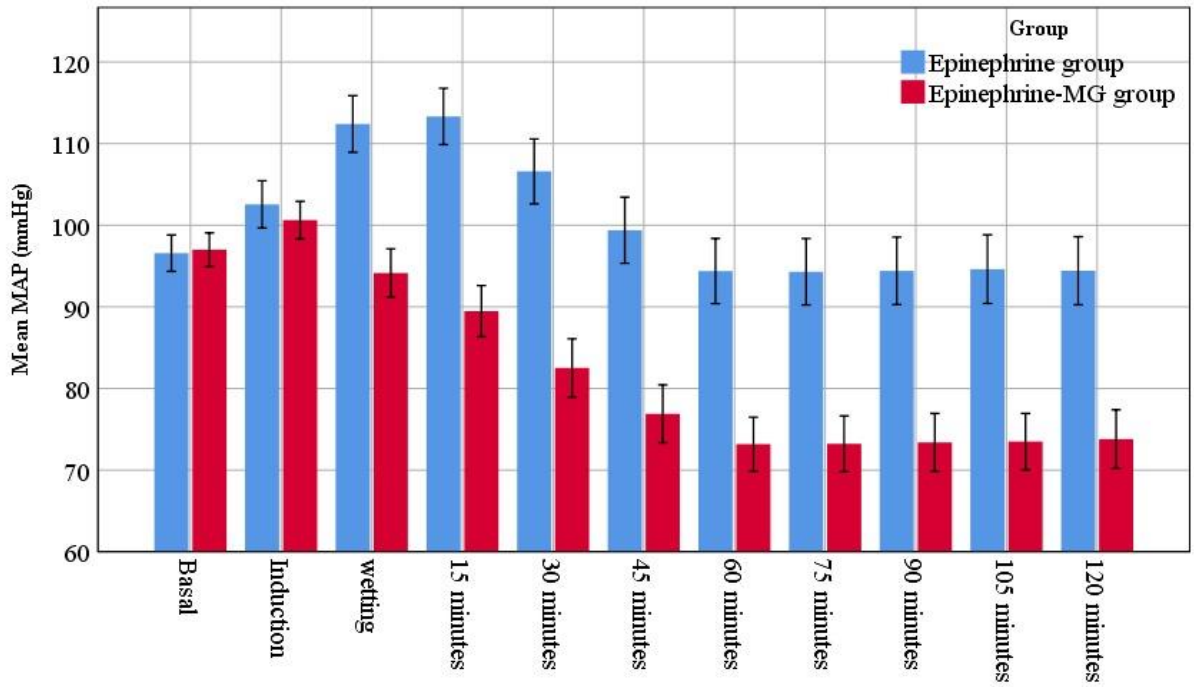

Figure [3]: Basal and intra-operative MAP in the study groups.

Table [2]: Incidence and types of cardiac arrhythmia in the study groups.

Arrhythmia	Epinephrine group	Epinephrine-Mg group	P value
None	55.3% [26]	70.2% [33]	0.077
Sinus tachycardia	36.2% [17]	29.8% [14]	
PVCs	8.5% [4]	0.0% [0]	

Table [3]: Intra-operative isoflurane consumption and post-operative morphine consumption in the study groups.

Variable	Epinephrine group	Epinephrine-Mg group	P value
Isoflurane consumption [ml]	97.87 ± 23.400	83.83 ± 19.732	0.002
Morphine consumption [mg]	2.09 ± 1.120	1.77 ± 0.960	0.141

DISCUSSION

In our study, there was no significant difference among both groups as regard basal and induction heart rates [p = 0.239 and 0.332, respectively]. However, starting from wetting until 120 min during operation, the epinephrine-Mg group had significantly lower heart rates compared to the epinephrine group [$p < 0.05$]. In concurrence with our results Stanbury stated that $MgSO_4$ prolongs recovery time of sinus node by indirect and direct inhibition on the sinoatrial node. While magnesium slows HR at rest by blockade of the sensitized membrane of the sympathetic ganglia. Also, Magnesium has a negative chronotropic effect after administration of atropine [15]. In another study by Jee *et al*. evaluating the effect of IV $MgSO_4$ on catecholamine release related to tracheal intubation. Comparison between; IV $MgSO_4$ 60 mg/kg, versus IV 0.09% sodium chloride over 1 min before intubation. They recorded plasma concentration of magnesium and catecholamine immediately before, during and immediately, and also 2 and 5 min after intubation. They demonstrated intubation induced no significant changes in HR while it caused a decrease in SBP and DBP, arterial blood pressure [15].

Conversely, other studies reported tachycardia with its administration [16]. The discrepancy between the results from different studies could be explained by a dose-dependent effect of magnesium on heart rate. In low doses, hypotension induced by magnesium sulfate could lead to reflex tachycardia. However, in large doses, inhibition of the Sino atrial node could explain bradycardia. Magnesium causes inhibition of the SA node via direct and indirect mechanisms; the direct mechanism is by decreasing the rate of SA node depolarization, and the indirect mechanism is via blockade of the cervical sympathetic ganglia [15].

In the present study, there was no significant difference among both study groups as regard both basal and induction mean arterial blood pressure readings [p = 0.778 and 0.295, respectively]. On subsequent readings, the epinephrine-Mg group showed significantly lower mean pressures compared to the epinephrine group [$p < 0.05$]. In a similar randomized controlled trial, Puri and Batra evaluated the effect of IV $MgSO_4$ 50 mg/kg on hemodynamics changes after tracheal intubation in patients with coronary artery disease scheduled for coronary artery bypass graft. They found that, $MgSO_4$ effectively prevented the rise in arterial blood pressure associated with endotracheal intubation [17].

Ryu et al. [17] has revealed that magnesium administration was accompanied by a significant decrease in blood pressure during anesthesia.

Over accumulation of calcium could lead to hypertension, vasospasm, and potentiation of vaso-constrictive drug action [11]. Also calcium has a major role in the release of catecholamines from the adrenal medulla and adrenergic nerve terminals in response to the stimulation by sympathetic nervous system. Magnesium competes with calcium for binding to the membrane channels. Hence, magnesium acts as a calcium antagonist and can modify the responses that mediated by calcium. Hence, $MgSO_4$ blocks release of catecholamine stores and decrease responses to adrenergic stimulations [11]. The previous facts could explain our findings regarding the effect of MgSO4 on blood pressure.

In our study, the epinephrine group had more cases with sinus tachycardia and premature ventricular contractions compared to the other group. The role of magnesium supplementation in the prevention of arrhythmia is proved, especially in patients with congestive heart failure. It mediates its action via its influence on other ions across the cell membrane, as mentioned previously [11].

Based on Naghipour et al. study, prophylactic Mg decreased all type of arrhythmias such as AF, VF, VT, and junctional rhythm in cardiac patients undergoing coronary artery bypass surgery [16]. By harmony with their results, Tiryakioglu *et al*. study showed the effectiveness of prophylactic use of $MgSO_4$ at preventing arrhythmia that may follow coronary bypass operations [18]. In addition, Toraman *et al*. concluded that the effectiveness in the preoperative and early postoperative periods of magnesium sulfate in reducing the incidence of AF after CABG [19]. In contrary, Cook *et al*. [20] conducted a meta-analysis to identify the effect of Mg to prevent postoperative AF. They found that prophylactic Mg did not have a beneficial effect to prevent postoperative AF after cardiac surgery, but their results attributed to take AF as a secondary end point.

All of the previous studies support our findings regarding the reduced incidence of arrhythmias in the epinephrine-Mg group despite its insignificance. This can be clarified by the dose of $MgSO_4$ infused in our study; 1 gm $MgSO_4$ led to a significant reduction in mean blood pressure, and heart rate but not significantly effective to decrease incidence of arrhythmia.

In the present study, isoflurane consumption decreased significantly in the epinephrine-Mg group compared to epinephrine group [83.83 vs. 97.87 ml, respectively – p = 0.002]. Magnesium has been reported to enhance the action of local anesthesia, and to produce general anesthesia. Additionally, it has sedative effects [21-22]. Magnesium contributes to the anesthetic action by multiple mechanisms such as N methyl D aspartate [NMDA] antagonism, blocking sympathetic overstimulation, and decreasing surgical stress response [22]. Olgun et al. [23] has reported that $MgSO_4$ administration was associated with a significant decrease in inhalational anesthesia requirements [p = 0.005]. Desflurane had mean values of 46.7 and 59.9 ml in magnesium and saline groups, correspondingly.

Not only with inhalational anesthetics, the administration of magnesium was associated with a marked decrease in the needs of total intravenous anesthesia, including propofol, remifentanil, and vecuronium [17]. On the contrary, another study reported no significant impact of $MgSO_4$ on inhalational anesthetic consumption [p > 0.05]. However, it led to a significant reduction in the muscle relaxant dose [24].

When it comes to morphine consumption in our study, although it decreased in the epinephrine-Mg group in comparison with the other group [1.77 vs. 2.09, respectively], there was no significant change among both groups. The decreased morphine consumption in the epinephrine-Mg group is attributed to its NMDA antagonistic action together with its antinociceptive effects [25]. Olgun and colleagues reported that morphine consumption was decreased in the group received $MgSO_4$ [25.9 vs. 33.2 mg in the other group]. Nevertheless, that difference was statistically significant [p = 0.048] [23].

Our study has a point of strength, and that is because it discussed a new therapeutic option to decrease epinephrine mediated cardiovascular side effects during a common plastic procedure. On the other hand, being a single center study is still a limitation. Trial different methods of administration with different dosage regimen also needed. Therefore, more studies including more cases from different centers should be conducted sooner.

Conclusion: Based on our findings, intravenous administration of 1 gm of $MgSO_4$ decreases heart rate, blood pressure, and inhalational anesthesia consumption during liposuction. However, it has no significant impact neither on the incidence of arrhythmia, nor morphine consumption. Despite that, the latter two variables need more studies to be more clarified. It is recommended to administer i.v. MgSO4 during liposuction, especially in large volume cases that will have more adrenaline dose in the wetting solution.

Financial and Non-financial Relationships and Activities of Interest

None

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