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Intravenous magnesium sulfate improves orotracheal intubation conditions: A randomized clinical trial

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ABSTRACT

Background: Muscle relaxation facilitates orotracheal intubation, but in some situations, neuromuscular blocking agents may be contraindicated.
Aim: To study the effect of intravenous magnesium sulfate perfusion before induction on orotracheal intubation conditions and the pressor response upon intubation.
Methods: This prospective, randomized, double-blind trial compared magnesium sulfate with saline solution as a placebo. The patients were randomized into two groups: the magnesium group (Group Mg+), which received 50 mg/kg of magnesium sulfate in 100 ml of saline 15 min before induction of anesthesia, and the saline group (Group Mg-), which received only 100 ml of saline 15 min before induction of anesthesia without magnesium sulfate. The induction in both groups was performed without neuromuscular blocking agents.
Intubation conditions in both groups were compared using the Copenhagen consensus conference: ease of laryngoscopy, vocal cord position and/or movement, and response to intubation or cuff (cough or diaphragmatic movement). Intubation conditions were considered acceptable (excellent or good) or unacceptable (poor). Systolic, diastolic arterial pressures and heart rate were also recorded during the study.
Results: In total, 76 patients (38 in each group) were included in this study. Clinically acceptable intubation conditions were significantly more observed in the magnesium group Mg + compared to the saline group Mg-: 36 patients (95 %) vs. 15 patients (39 %) ($P < 0.001$).
Hemodynamic stability was more observed in the magnesium group, with a statistically significant lower heart rate throughout Mg + compared to the saline group.
Conclusion: Administration of magnesium sulfate before induction of anesthesia significantly improved intubation conditions without the need for neuromuscular blocking agents.

1. Introduction

The usual method for orotracheal intubation relies on direct laryngoscopy following induction of anesthesia. Neuromuscular blocking agents are widely recognized as an effective means to facilitate intubation, significantly improving its conditions and minimizing laryngeal complications [1,2]. Despite their effectiveness, neuromuscular blockers are not without risks and can lead to complications such as anaphylaxis, intraoperative memorization, and residual neuromuscular blockade [3] Recent studies have explored alternative approaches to tracheal intubation without the use of neuromuscular blocking agents, such as propofol mixed with various opioids [4–9] or the administration of adjuncts like lidocaine and midazolam [5,6] Magnesium, an essential mineral in the human body, has gained increasing attention in anesthesia practice due to its role in physiological processes, especially muscle relaxation [10] In this study, we aim to investigate the efficacy of 50 mg/kg of magnesium before anesthetic induction in improving intubation conditions without neuromuscular blocking agents while monitoring hemodynamic variations and assessing the occurrence of adverse effects due to magnesium use.

2. Materials and methods

A double-blind randomized clinical trial was conducted following

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ethical approval (no. 0505/2023). The study was carried out in accordance with the Good Clinical Practice guidelines and adhered to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. We included patients aged between 20 and 65 who were scheduled for elective surgery that required orotracheal intubation with an American Society of Anesthesiology (ASA) status of I or II, in the absence of anticipated difficult intubation criteria. Non-inclusion criteria included procedures exceeding a duration of 3 h, urgent surgical interventions, full stomach patients, anticipated difficult intubation, renal diseases, respiratory insufficiency, neuromuscular disorders, morbid obesity (defined as a Body Mass Index BMI >40), and known allergies to magnesium sulfate. Unanticipated difficult intubation, unplanned prolonged operations exceeding 3 h, and non-compliance with the chosen anesthesia protocol were excluded. The anesthetic protocols were explained to the patients during the pre-anesthetic visit. Patients were assigned to one of the two groups to receive a perfusion of magnesium sulfate or saline solution before induction of anesthesia using an online random list generator (https://www.random.org). (The online random list generator create a random sequence of numbers corresponding to the treatment groups, Specify the range of numbers and the number of random numbers we need, then we Assign Participants to Treatment Groups based on the random sequence generated). Magnesium group (Mg+): Patients received a pre-induction infusion of 50 mg/kg of magnesium sulfate (based on ideal body weight) dissolved in 100 ml of normal saline over 15 min. Saline group (Mg-): Patients receive a pre-induction infusion of 100 ml of normal saline over 15 min, without magnesium sulfate. The study was conducted by two anesthetists. The first prepared the syringes following strict aseptic techniques, while the second was tasked with perioperative and postoperative monitoring. The same anesthesia procedures were applied to all patients. The patient monitoring included continuous electrocardiographic surveillance with a 5-lead setup, monitoring of heart rate (HR), respiratory rate, pulse oximetry for oxygen saturation (SpO2), non-invasive or invasive blood pressure (BP) depending on the procedure, and end-tidal carbon dioxide pressure (PetCO2) measurement following patient intubation. Patients were placed in the supine position with their heads on a pillow. An intravenous line with an 18-gauge cannula was secured, and administration of 0.3 mg/kg of midazolam occurred 5 min after establishing venous access. Then, an infusion of 500 ml of normal saline with the addition of either 100 ml of normal saline or 50 mg/kg of magnesium sulfate in 100 ml of saline over 15 min. After 3 min of preoxygenation, general anesthesia was induced with 3 μg/kg of fentanyl, followed by 3 mg/kg of propofol, and then orotracheal intubation was performed using an appropriately sized and weighted endotracheal tube by an experienced anesthesiologist who was not involved in the study. Orotracheal intubation was done using a Macintosh laryngoscope. No ventilation was performed unless the patient desaturated with SpO2 ≤ 90 %. Episodes of desaturation were recorded for each patient. The total apnea time was also noted (from the end of the injection of anesthetic agents until connection to the ventilator and the appearance of 3 cycles of capnography). We assessed intubation conditions using the Copenhagen score [11], which is based on the ease of laryngoscopy, position and/or movements of the vocal cords, and reaction to intubation (diaphragmatic movement or coughing). Laryngoscopy was categorized as easy (jaw relaxed, no resistance to the laryngoscope blade), feasible (jaw not fully relaxed, slight resistance to the blade), or difficult (poor jaw relaxation, active resistance from the patient to laryngoscopy). Intubation conditions were categorized as excellent (all qualities were excellent), good (all qualities were either excellent or good), and poor (the presence of a single quality listed under poor).

Intubation conditions rated as excellent or good were considered clinically acceptable, while those rated as poor were deemed clinically unacceptable. If intubation was not achieved within 60 s due to unforeseen poor intubation conditions, 1 mg/kg of succinylcholine (based on real weight) was administered intravenously, and intubation was performed again 1 min later. Severe coughing occurring after intubation was treated with an additional bolus of propofol (3 mg/kg). If during laryngoscopy, Cormack-Lehane grade 3 or 4 was encountered and intubation was not successful after succinylcholine administration, the algorithm for unanticipated difficult intubation was initiated, and the patient was excluded from the study. After intubation, a volume-assisted controlled ventilation strategy was employed, and parameters were modulated to maintain a PET CO2 of 35–40 mmHg. The induction of anesthesia was then completed with 0.15 mg/kg cisatracurium and maintained using 0.05–0.2 μg/kg of remifentanil and an inspired sevoflurane concentration of 2–3% in a 50 % oxygen/air mixture. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and heart rate (HR) were recorded upon entering the operating room, before themagnesium/saline infusion, before induction, after intubation, at 1 and 2 min post-intubation, then every 2 min for 10 min, followed by measurements every 10 min for up to 60 min, then at extubation. A bolus of nicardipine (0.5–1 mg) was administered when SAP>150 mmHg; a bolus of 3 mg of ephedrine was administered to maintain SAP>80 mmHg; and 0.5 mg of atropine was used when HR was <50 beat/min. Thirty minutes before extubation, 1 g of paracetamol along with 20 mg of nefopam were administered intravenously over 30 min. The presence of coughing while emerging from anesthesia was noted during extubation. Patients were then transferred to the post-anesthesia care unit (PACU), where their vitals (HR, SAP, and DAP) were recorded every 30 min for 2 h. Adverse effects of magnesium sulfate (nausea/vomiting, diarrhea, epigastric pain, rhythm disturbances, hypertension, and hypersensitivity reactions) were noted during the infusion of the prepared solution and for 2 h in the post-anesthesia care unit (PACU). In each group, a total of 34 patients were required to obtain a difference of 30 % in the clinical acceptability of intubation conditions between the two groups with a study power of 0.8 and $\alpha = 0.05$. Taking into consideration possible dropouts, it was decided to include 40 patients per group. All variables, including basic characteristics, were presented as a number with a percentage for qualitative variables, as mean ± standard deviation for quantitative variables following a normal distribution, and as a median with 25th and 75th percentiles for quantitative variables not following a normal distribution. The normal distribution was evaluated with the Kolmogorov-Smirnov test. Categorical data were analyzed using the chi-square or Fisher statistical tests, and quantitative variables were analyzed using the Student's t-test or Mann-Whitney *U* test. Statistical significance was established at $p < 0.05$ (two-tailed). Data entry and statistical analysis of the data were performed using Statistical Package for Social Sciences (SPSS) for Windows version 26.

3. Results

The study was conducted over a period of six months, from April 2023 to September 2023.

Eighty-four patients were initially eligible for the study, and a total of 76 patients successfully completed the study and were analyzed (Fig. 1). Demographic and intubation characteristics were comparable between the two groups (Table 1). The types of surgeries are distributed statistically equally between the two groups (Table 2). Intubation conditions were comparable in all patients. Ventilation with a face mask was easy for all patients. The number of patients with excellent or good intubation conditions was significantly higher in group Mg + than in group Mg- based on the Copenhagen conference score [11]. Laryngoscopy was easy for 37 patients (97 %) in the magnesium group vs. 25 patients (66 %) in the saline group ($P < 0.001$). Thirty-three patients (87 %) had an optimal vocal cord position (abduction position) in the magnesium group compared to 16 patients (42 %) in the saline group ($P < 0.001$). The saline group showed a higher percentage of patients who sustained coughing during intubation: 34 % (13 patients) vs. 3 % (1 patient) in the magnesium group. Clinically acceptable intubation conditions were observed with a significantly higher frequency in the magnesium group compared to the saline group: 36 patients (95 %) vs. 15 patients (39 %) ($P < 0.001$). Excellent intubating conditions were noted in 25 patients

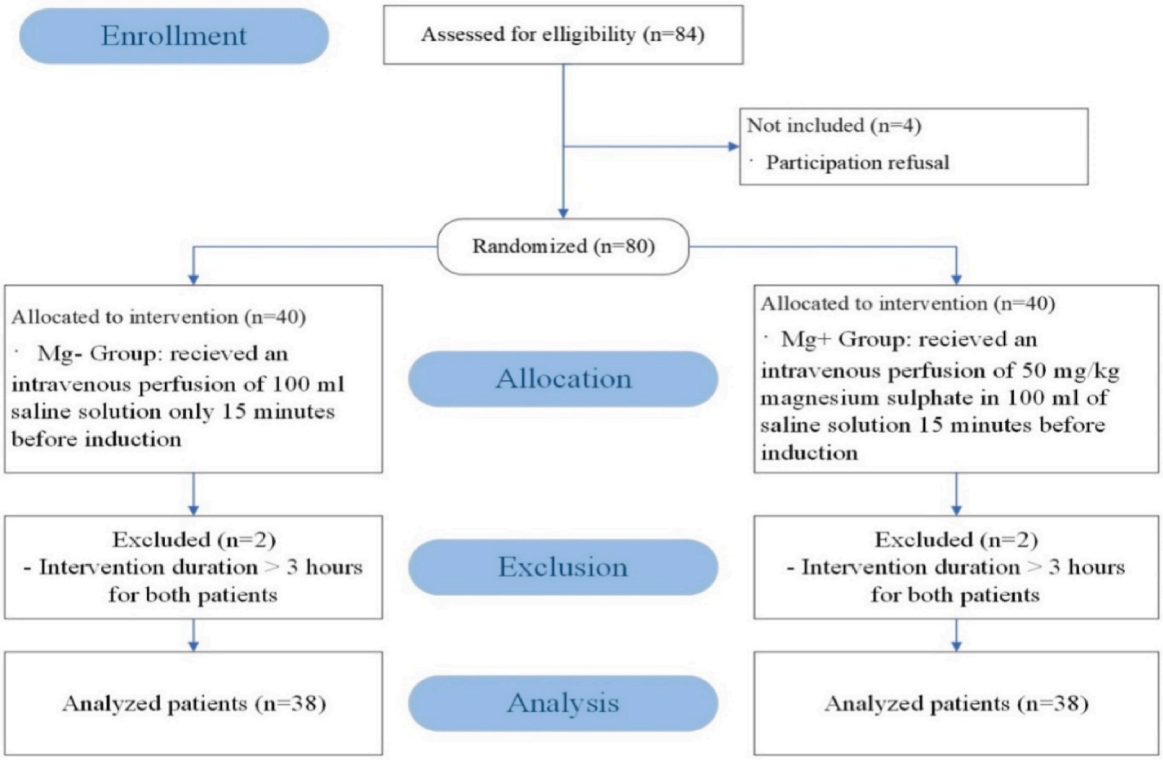

Fig. 1. Flowchart of the study.

Table 1
Patient demographic and morphological characteristics.

Main features	Group Mg- (n = 38)	Group Mg+ (n = 38)	P value
Age (years)	45,74 [24–64]	43,05 [20–64]	0.246[a]
BMI (kg/m^2)	26.39 ± 3.83	25.74 ± 2.44	0.381[c]
Sex (M/F)			
-Masculine	16 (42.1 %)	20 (52.6 %)	0.358[b]
-Feminine	22 (57.9 %)	18 (47.4 %)	
ASA Status (I/II)			
- ASA I	33 (86.8 %)	33 (86.8 %)	1[b]
-ASA II	5 (13.2 %)	5 (13.2 %)	

Group Mg-: Saline group; Group Mg+: Magnesium group; ASA: American Society of Anesthesiologists; BMI: Body Mass index.
[a] Mann–Whitney *U* test.
[b] Chi-squared test.
[c] Student *t*-test.

Table 2
Comparison of types of surgeries between the two groups.

	Group Mg-(n = 38)	Group Mg+ (n = 38)	P value
ORL surgeries (number/poucentage)	3/8 %	3/8 %	1[b]
Abdominal and proctologic surgeries (number/percentages)	23/61 %	24/63 %	0.876[a]
Orthopedic (number/percentages) surgery	12/32 %	11/29 %	0.754[a]

Group Mg-: Saline group; Group Mg+: Magnesium group; ORL: oto-rhino-laryngology.
[a] Chi-squared test. .
[b] Fisher test.

(66 %) compared to two patients with excellent conditions in the saline group (5 %) (P < 0.001) (Table 3).

Administration of suxamethonium was necessary in one patient in the magnesium group and six patients in the saline group (P = 0.108).

Table 3
Intubation conditions.

	Magnesium group (n = 38)	Saline group (n = 38)	P value
Laryngoscopy			<0.001[a]
Excellent (easy)	37 (97 %)	25 (66 %)	
Good (feasible)	1 (3 %)	8 (21 %)	
Poor (difficult)	0 (0 %)	5 (13 %)	
Vocal cord position			<0.001[a]
Excellent (abduction)	33 (87 %)	16 (42 %)	
Good (intermediate)	3 (8 %)	13 (34 %)	
Poor (closed)	2 (5 %)	9 (24 %)	
Reaction to endotracheal tube insertion			<0.001[a]
Excellent (no reaction)	27 (71 %)	10 (26 %)	
Good (1–2 movement <5s)	10 (26 %)	15 (39 %)	
Poor (more than 2 movements or >5s)	1 (3 %)	13 (34 %)	
Intubation conditions			<0.001[a]
Excellent	25 (66 %)	2 (5 %)	
Good	11 (29 %)	13 (34 %)	
Poor	2 (5 %)	23 (61 %)	
Clinically Acceptable	36 (95 %)	15 (39 %)	

Excellent: all qualities are excellent; Good: all qualities are excellent or good; Poor: at least one quality is poor.
Values are number (%).
[a] Chi-squared test. Group Mg-: Saline group; Group Mg+: Magnesium group.

There was no intubation failure. The hemodynamic variations were similar between the two groups after induction and then after intubation and at extubation in terms of HR, SAP, and DAP (P > 0.05 for all three parameters). At 1 min after intubation and during the first hour of the intervention, HR became significantly lower and more stable in the magnesium group than in the saline group (P < 0.05). Atropine was used for six patients in the saline group. Both SAP and DAP were similar in the two groups from 1 min to 40 min (P > 0.05), with significantly lower values recorded at 50 and 60 min for both parameters in the magnesium group than in the saline group (P < 0.05 for both). Ephedrine bolus (3

mg) was more commonly used in the saline group (Table 4), although the variation of SAP and DAP were not statistically significant (Fig. 2).

Post operative hemodynamic variations were comparable in the two groups (Table 5).

No adverse effects of magnesium or complication of magnesium use were recorded in the two groups.

4. Discussion

The aim of our research was to study the effect of 50 mg/kg of intravenous magnesium sulfate perfusion before induction on orotracheal intubation conditions and the pressor response to intubation. Ease of laryngoscopy, vocal cord position, and reaction to tube insertion and cuff inflation were recorded. Clinical acceptability was then determined based on those parameters. HR, SAP, and MAP were also recorded during the intervention.

Intubation conditions were significantly more clinically acceptable in group Mg + than in group Mg-. In the magnesium group, laryngoscopy was significantly easier, vocal cords were significantly more abducted, and there were fewer reactions to intubation compared to the saline group. Hemodynamic stability was also more observed in the magnesium group than in the saline group. Magnesium is the fourth essential mineral in the human body. It plays a crucial role in cellular functions such as energy utilization, metabolism, and storage [12].

Additionally, it acts as a cofactor in essential physiological processes, including neuromuscular function, protein synthesis, and genetic material stability [13,14]. Magnesium influences membrane potential by modulating sodium and potassium currents [15].

Moreover, it exerts a modulatory effect on the central nervous system by antagonizing the NMDA receptor, contributing to analgesia. It also affects the adrenal medulla, decreasing the release of catecholamines and thereby imparting an indirect vasodilatory action. This action is coupled with its direct vasodilatory effect by reducing vasopressin-induced vasoconstriction. In our investigation, the primary impact of magnesium sulfate explaining the enhancement of intubating conditions appears to be its influence on the neuromuscular junction. In terms of magnesium-induced myorelaxation, the inhibition of calcium-mediated acetylcholine release from the presynaptic gap at the neuromuscular junction is pivotal. A reduction in postsynaptic acetylcholine sensitivity, along with its direct impact on myocyte membrane potential, may also play a role [16]. Administering magnesium sulfate induces generalized muscle relaxation, particularly at the pharyngolaryngeal level, thus facilitating orotracheal intubation. Our study found that intubation conditions were largely improved after adjunction of magnesium sulfate before induction, which made vocal cord movements and coughing less

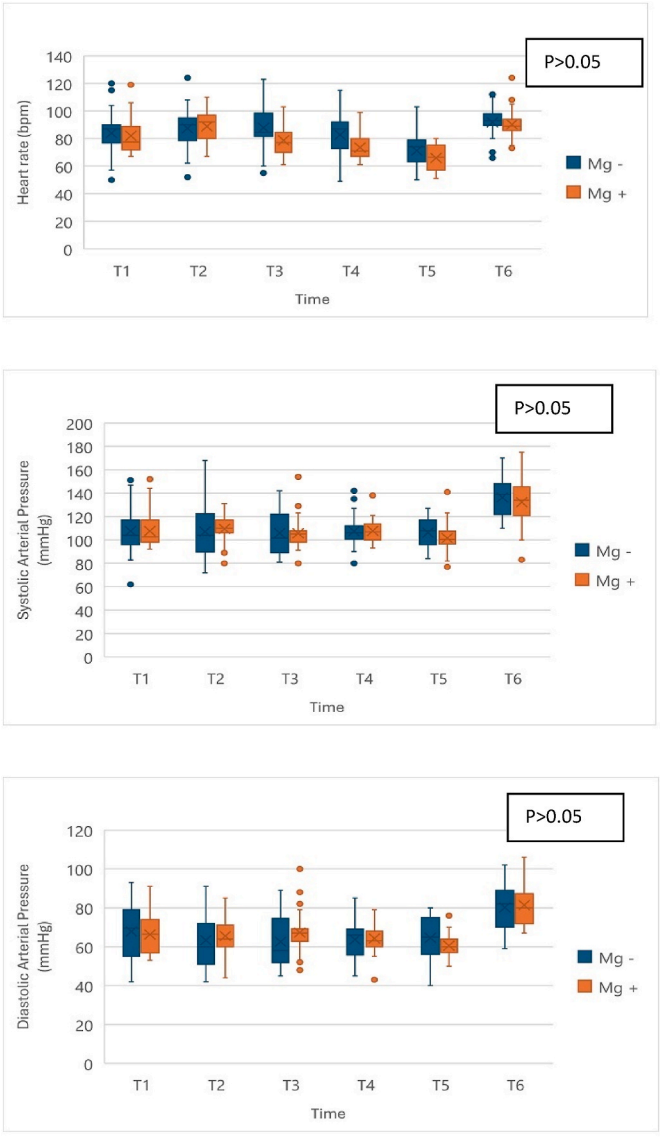

Fig. 2. Hemodynamic variations.

Table 4
Comparision of need of ephedrine between the groups.

Mg-Group (n = 38)			Mg + Group (n = 38)		p
	Number of patients needed ephedrine (3 mg)	%	Number of patients needed ephedrine (3 mg)	%	
Before induction	0	0 %	0	0 %	
after Induction	4	11 %	0	0 %	0,04[a]
After Intubation	10	26 %	2	5 %	0,01[a]
1 min	3	8 %	3	8 %	0,947[a]
2 min	6	16 %	5	13 %	0,668[a]
4 min	2	5 %	1	3 %	0,562[a]
6 min	2	5 %	1	3 %	0,562[a]
8 min	6	16 %	1	3 %	0,044[a]
10min	1	3 %	0	0 %	0,321[a]
20min	5	13 %	1	3 %	0,083[a]
30min	4	11 %	2	5 %	0,39[a]
40min	3	8 %	3	8 %	1[a]
50min	4	11 %	3	8 %	0,708[a]
60min	0	0 %	2	5 %	0,168[a]
Extubation	0	0 %	0	0 %	

n:number; % pourcentage.
[a] : Fisher test; Mg- Group: saline Group; Mg + Group: Magnesuim Group.

Table 5
Comparison of post operative hemodynamic variation between the two groups.

Mg- Groupe (n = 38)		GroupeMg+ (n = 38)	p
SAP AT the entry of PACU	140 ± 14	136 ± 15	0,319[a]
DAP at the entry of PACU	82 ± 11	82 ± 11	0,894[a]
SAP30min PACU	134 ± 14	130 ± 12	0,213[a]
DAP 30min PACU	80 ± 14	78 ± 10	0,350[a]
SAP60minPACU	129 ± 10	127 ± 11	0,567[a]
DAP60minPACU	78 ± 9	78 ± 8	0,889[a]
SAP90minPACU	126 ± 9	126 ± 9	0,820[a]
DAP90minPACU	78 ± 9	78 ± 6	0,875[a]
SAP 120minPACU	123 ± 10	121 ± 8	0,271[a]
DAP 120minPACU	76 ± 9	75 ± 7	0,487[a]

SAP: systolic arterial pressor; DAP: Diastolic arterial pressor; PACU: post anesthesia care unit; Mg- Group: saline Group; Mg + Group: Magnesuim Group.
[a] Student test.

likely when intubating patients. This is consistent with the findings of Aissaoui et al. [17], who conducted a study involving 60 patients divided into two groups to evaluate the effect of 45 mg/kg of magnesium sulfate in the magnesium group 10 min before anesthetic induction on intubation conditions compared to a control group that only received saline solution before induction. The results showed a significantly higher number of patients with excellent or good intubation conditions in the magnesium group than in the control group: 25 vs. 18 patients (83 % vs. 60 % of cases). Another study by Soltani et al. [18], including 100 patients scheduled for ophthalmic surgery, was conducted to investigate the role of magnesium sulfate in facilitating orotracheal intubation without the need for neuromuscular blocking agents. This study showed that magnesium sulfate does improve intubation conditions by shortening the time required for laryngoscopy as well as reducing vocal cord movements and the emergency use of muscle relaxants. Rizvanovic et al. [19] compared intubation conditions with and without muscle relaxation in 80 children and found that anesthetic induction combining propofol and fentanyl secured acceptable intubation conditions comparable to those with suxamethonium. While they do have adverse effects, neuromuscular blocking agents remain of importance as choosing not to use them comes with a high price: poor intubation conditions, difficult airways, laryngeal injuries, and postoperative hoarseness, and it is proven that they do offer the best intubation conditions [20,21]. Magnesium (Mg2+) plays a significant role in maintaining the physiological functions of cardiac tissue through vasodilation, reducing vascular resistance, improving blood circulation, preserving myocardial electrical properties, and its anti-inflammatory activity [22–24]. Magnesium also inhibits platelet aggregation and adhesion [25]. This mineral acts as an antagonist to α-adrenergic receptors and can lead to a transient decrease in blood pressure associated with peripheral vasodilation [26]. However, despite its vasodilatory properties, magnesium generally does not cause significant hypotension in normotensive patients due to a concomitant increase in cardiac output [27]. Our results have shown that magnesium sulfate administered 15 min before induction significantly improves hemodynamic stability in the magnesium group compared to the saline group during the first hour of the surgical procedure. The heart rate (HR) then became significantly more stable in the Mg + group. Puri et al. [28] administered a dose of 40 mg kg-1 of magnesium sulfate to attenuate the cardiovascular response to tracheal intubation. Their findings revealed a reduction of 17 % in mean arterial pressure (MAP) and a decrease of 25 % in systemic vascular resistance following magnesium administration. Our study has shown a similarity between the two groups in terms of systolic and diastolic arterial pressures, starting after anesthetic induction and continuing until the 50th and 60th minutes of the intervention, where the difference became significant in the magnesium group with more stable values. Our study also showed that the heart rate (HR) was significantly lower and in the normal range in the magnesium group than in the saline group. This study had some limitations. The first limitation is the controversy surrounding the technique itself, which involves intubation without neuromuscular blocking agents. Those drugs come with potential adverse effects such as malignant hyperthermia, hyperkalemia, and anaphylaxis [29,30]. In order to avoid such complications, intubation without myorelaxation has emerged and become a clinical practice. Another limitation to our study is that the selected population is composed of mostly healthy patients of status ASA I or II that are scheduled for elective surgery, and it did not include emergencies that sometimes need crush induction without muscle relaxants for various possible reasons, like high blood potassium levels. We also recognize there were multiple surgeries in our study, in fact some surgeries can provide more hemodynamic variability than others, however, patients were randomized in the two groups and kind of surgeries were comparable in the two groups.

5. Conclusion

We conclude that, magnesium sulfate is an effective drug to use as an adjuvant for tracheal intubation without needing neuromuscular blocking agents. Patients receiving IV magnesium experienced easier laryngoscopy and better intubation conditions, with 95 % clinically acceptable conditions in the magnesium group. The dosage used in this study (50 mg/kg) did not cause any significant adverse hemodynamic effects or post-operative complications. This approach could be beneficial, especially for patients unable to use neuromuscular blocking agents.

CRediT authorship contribution statement

Imen Zouche: Methodology, Investigation, Conceptualization. **Wassim Guermazi:** Funding acquisition, Formal analysis, Data curation. **Faiza Grati:** Software, Project administration, Funding acquisition. **Mohamed Omrane:** Formal analysis, Data curation. **Salma Ketata:** Writing – original draft, Supervision, Project administration. **Hichem Cheikhrouhou:** Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tacc.2024.101371.

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