

ORIGINAL RESEARCH

ANESTHESIOLOGY

The effect of adding magnesium sulfate to low dose rocuronium on neuromuscular blockade and anesthesia for direct laryngoscopy: A randomized controlled trial

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Abstract

Background: Direct laryngoscopy is a day case procedure used for diagnosis and sometimes in treatment of laryngeal tumors. It is a short procedure that requires complete relaxation and rapid recovery. Rocuronium emerged as a good alternative to succinylcholine with better profile. Adding magnesium sulphate (MgSO₄) to rocuronium can accelerate its onset of action with better relaxation. The aim of this study is to investigate the effect of MgSO₄ when added to low dose of rocuronium on neuromuscular blockade and anesthetic profile.

Methodology: Sixty ASA I-II patients, scheduled for direct laryngoscopy were randomly allocated to group R: received rocuronium dose of 0.6 mg/kg and group RM: low dose rocuronium 0.4 mg/kg and MgSO₄ 50 mg/kg.

Results: RM group showed shorter onset, and less time to achieve deep level of neuromuscular blockade but prolonged duration when compared to R group (P value = 0.035, <0.001 and <0.001 respectively). Heart rate, mean arterial blood pressure and BIS values were lower in RM group compared to R group.

Conclusions: Adding MgSO₄ to low dose rocuronium hastens its onset of action and shorten the time needed to achieve deep blockade but with prolonged duration. It had a favorable anesthetic profile when compared to conventional anesthesia.

Key words: Magnesium sulfate, rocuronium, neuromuscular blockade, anesthesia.

Trial registration: The trial was registered at ClinicalTrials.gov with registration number (NCT 04510337) <https://clinicaltrials.gov/ct2/show/NCT04510337>.

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1. Introduction

Clinical staging of cancer larynx using direct laryngoscopy is performed under general anesthesia for accurate determination of tumor extent and proper pathological diagnosis.¹ Direct laryngoscopy with excisional biopsy has a therapeutic role in management of hyperplastic epithelial lesions of the larynx.² It is a day case procedure done under general anesthesia.³ Operating through the larynx carries an anesthetic challenge of being a shared airway procedure.⁴

Although it is a short procedure, but it needs full relaxation and rapid recovery. Succinylcholine was the muscle relaxant of choice for such procedures because of its rapid onset, short duration and full relaxation effect.⁵ Rocuronium evolved as a better choice with less side effects and longer duration of action.⁵ Addition of magnesium sulphate (MgSO₄) to low dose rocuronium can accelerate rocuronium onset of action and obtain good relaxation with shorter muscle relaxant duration,⁶

shorter onset of action can be attributed to the effect of $MgSO_4$ on decreasing the median effective dose of non-depolarized muscle relaxants.⁷ Additionally, $MgSO_4$ effectively attenuates the hemodynamic response to

Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Eighty-six cancer patients referred to the anesthesia department in our institute requiring direct laryngoscopy for staging and diagnosis of laryngeal cancer were assessed for eligibility in preoperative anesthesia clinic, 26 patients were excluded, 19 of them did not meet the inclusion criteria and 7 refused to participate. Sixty patients were randomly allocated using closed envelop method into one of the two study groups by anesthesia resident in the holding area. (Figure 1) Random number list was generated using computer generated random list. The study included American Society of Anesthesiologist (ASA) I and II cancer patients with laryngeal tumors aged from 30 to 70 years. Patients with renal or hepatic insufficiency, neuromuscular disease, known allergy to any of the study drugs as well as large glottic and/or supra-glottic lesions with or without breathing difficulties were excluded from the study.

Routine preoperative assessment was conducted as standard (complete blood count, liver and kidney function tests, coagulation profile and chest x-ray) in addition to indirect laryngoscopy airway assessment. Upon arrival to the holding area all the patients were monitored by standard monitoring (electrocardiogram, pulse oximetry and non-invasive automated arterial blood pressure), all patients had a 20 G cannula inserted. On arrival to the operating theatre Group R: received 100 ml saline infusion 15 min prior to induction of anesthesia and Group RM: received 100 ml saline with 50 mg/kg $MgSO_4$ infusion 15 min prior to induction of anesthesia. Induction of anesthesia was done with propofol 2 mg/kg and fentanyl 2 μ /kg. Then Group R: received rocuronium 0.6 mg/kg and Group RM: received rocuronium 0.4 mg/kg followed by single lumen endotracheal intubation by an expert anesthesiologist who was blind to the study group. Anesthesia was maintained using controlled mechanical ventilation with 50% Fio₂, and sevoflurane to achieve end tidal MAC 2-3% according to each patient hemodynamic response, top up doses of rocuronium 0.15 mg/kg were given as needed to keep at least 3 TOF responses suppressed. Starting from induction of anesthesia heart rate (HR) and oxygen saturation (Spo₂) were continuously monitored, mean arterial blood pressure (MAP) were measured every 5 min. In case of elevation of MAP or HR $\geq 20\%$ from baseline, a rescue fentanyl of 25 μ g was given and reported.

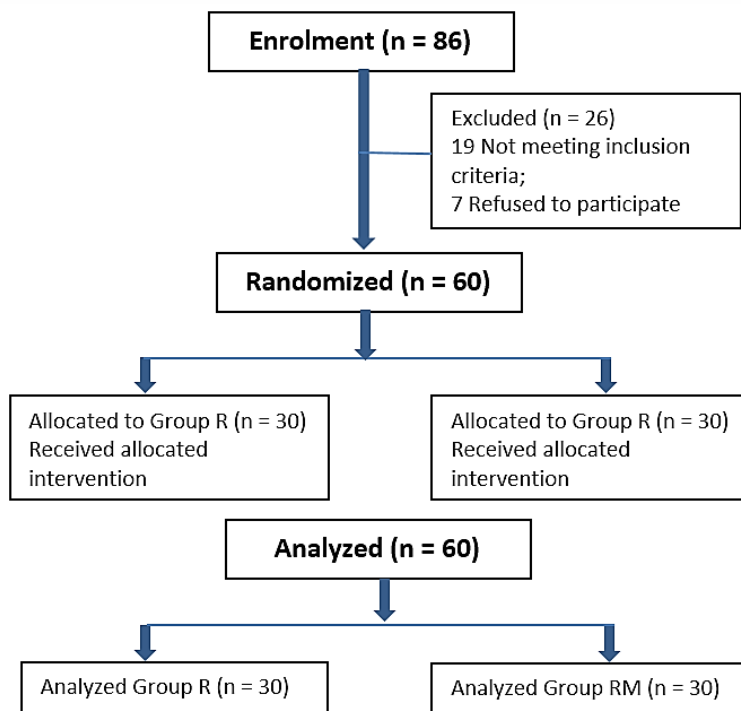


Figure 1: CONSORT diagram

laryngoscopy and endotracheal intubation.⁸ The use of $MgSO_4$ as an anesthetic adjuvant has been increasingly introduced in anesthetic management secondary to its role in inhibiting catecholamine release and as a calcium channel antagonist as well as its N- methyl D aspartate (NMDA) antagonist.^{9,10} The aim of this study is to investigate the effect of magnesium sulphate when added to low dose of rocuronium on neuromuscular blockade action and anesthetic management.

2. Methodology

Formal approval of the Institutional Review Board of the National Cancer Institute, Cairo University (IRB 201617031.2P) was obtained and the trial was registered at clinicaltrials.gov (NCT 04510337) <https://clinicaltrials.gov/ct2/show/NCT04510337>.

This double blinded (participant and assessor) was done in the period from April 2018 to February 2021 after a written informed consent taken from all patients enrolled in the study. The study was conducted according to the principles of the Declaration of Helsinki and followed

Intubating conditions were assessed according to good clinical research practice¹¹ from excellent to poor using ease of laryngoscopy, vocal cord position and/or movement and response to intubation or cuff inflation (cough or diaphragmatic movement). Intubating conditions were considered as acceptable (excellent or good) or unacceptable (poor). (Table 1)

Electrodes were placed on the forehead to monitor bispectral index (BIS) (BIS™ LoC 2 Channel monitor, COVIDIEN llc, 15 Hampshire Street, Mansfield, MA, USA). BIS values were continuously monitored, and inhalational anesthetic mac value were adjusted accordingly to maintain values between 40-60. Neuromuscular block was monitored using accelomyography peripheral nerve stimulator [TOF-Watch® SX, Organon (Ireland) Ltd] measuring the response to ulnar nerve stimulation at the thumb using (2 Hz every 12 s). After induction of anesthesia onset of rocuronium was assessed by train of four (TOF) stimulation and was defined as reaching 95% suppression of TOF first twitch. Duration of action was defined as time from rocuronium injection to time to return of first TOF twitch. Post tetanic count was assessed after reaching TOF 0. Deep neuromuscular blockade was defined as PTC count ≤ 5 . At the end of the procedure extubation was done when TOF ratio ≥ 0.9 was attained, after reversal of rocuronium induced muscle relaxation by sugammadex (2 mg/kg) for moderate block (TOF ≥ 2) and 4 mg/kg for deep block (PTC ≤ 5). Recovery time from sugammadex injection to TOF 0.9 was assessed.

Our primary outcome was duration of muscle relaxant in minutes. Secondary outcomes were onset time, depth of blockade, intraoperative hemodynamics including HR, MAP, BIS values, intubating conditions, and recovery time.

Sample size calculation was based on the previous paper by Choi et al., 2017⁶, the difference between 2 groups in duration of neuromuscular blockade is 8 ± 7.5 min. Using power 95% and 5% significance level, 24 patients are required. We added 6 cases in each group to overcome drop out. Therefore, we recruited 30 patients in each group. Sample size calculation was achieved using PS: Power and Sample Size Calculation software Version 3.1.2 (Vanderbilt University, Nashville, Tennessee, USA).

Data were analyzed using IBM SPSS version 21 (SPSS Inc., Chicago, IL). Data were explored for normality using Shapiro-Wilk test and histograms. Numerical data were described as mean and standard deviation and were compared using the Student's t-test. Categorical data were described as numbers and percentages and were compared using the chi-square test and fisher exact as

appropriate. A two tailed p-value less than or equal to 0.05 was considered statistically significant.

3. Results

Patients' characteristics (age, weight, height, BMI, sex and ASA) were insignificantly different between both groups. (Table 2)

Onset time of neuromuscular blockade was significantly shorter in RM group compared to R group (85.63 ± 11.23 and 93.47 ± 16.42 sec. respectively, $p = 0.035$) and duration of neuromuscular blockade was significantly prolonged in group RM than group R (35.40 ± 4.12 and 30.70 ± 3.49 min. respectively, $p < 0.001$). There was significant difference in time needed to achieve deep block in RM group when compared to R group (10.77 ± 1.92 and 15.07 ± 2.70 min. respectively, $p < 0.001$). There was no significant difference in duration of surgery, duration of anesthesia and recovery time between both groups ($p = 0.233, 0.182, 0.104$ respectively). (Table 3) No patient in RM group versus 7 patients in R group needed a single dose of 25 μg rescue fentanyl ($p = 0.011$). (Table 4) Intubating conditions were better in RM group than R group although it was not statistically significant ($p = 0.237$). (Table 4)

Heart rate was significantly lower in RM group than R group at all time measurement except at baseline. (Figure 2)

Mean arterial blood pressure was significantly lower in RM group than R group at all time measurement except at baseline. (Figure 3)

Peripheral oxygen saturation was comparable in both groups at all time measurement. (Figure 4) BIS values were significantly lower in RM group than R group at all time measurement except baseline and end was insignificantly different between both groups. (Figure 5) Only two patients in MR group reported burning sensation during MgSO₄ infusion which resolved spontaneously.

4. Discussion

Monitoring neuromuscular block allows more precise muscle relaxant dose titration according to drug dose effect, as well as proper estimation of accurate timing for reversing the drug effect when needed.¹² Studies on different doses of rocuronium were conducted to assess different doses effect on intubating conditions.^{6,13,14} Obtaining rapid onset of muscle relaxant can be achieved by increasing the intubating dose, yet this would result in the drawback of longer duration.¹⁵ On the other hand, adding magnesium sulphate (MgSO₄) to rocuronium is thought to shorten the onset by inhibiting

Parameter	Intubating condition		
	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cords position	Abducted	Intermediate	Closed
Reaction to insertion of the ETT and cuff inflation (Diaphragmatic movement/coughing)	None	Slight	Vigorous

Demographic data **	Group R (n = 30)	Group RM (n = 30)	p value
Age (y)	54.20 ± 7.54	53.57 ± 7.91	0.752
Weight (kg)	77.10 ± 10.04	75.97 ± 11.44	0.685
Height (m)	1.67 ± 0.06	1.67 ± 0.05	0.949
BMI (kg/m ²)	27.64 ± 4.14	27.25 ± 4.58	0.731
Sex *			
Male	27 (90.0)	29 (97.0)	0.612
Female	3 (10.0)	1 (3.0)	
ASA physical status *			
ASA I	22 (73.3)	17 (65.7)	0.176
ASA II	8 (26.7)	13 (43.3)	

* Data are presented as Mean ± Standard Deviation; ** Data are presented as number (percent). BMI: body mass index, ASA: American Society of Anesthesiologists

Parameter	Group R (n = 30)	Group RM (n = 30)	p value
Duration of surgery (min)	31.63 ± 4.48	30.33 ± 3.85	0.233
Duration of anesthesia (min)	43.90 ± 3.33	42.83 ± 2.77	0.182
Onset time of NMB (sec)	93.47 ± 16.42	85.63 ± 11.23	0.035*
Duration of NMB (min)	30.70 ± 3.49	35.40 ± 4.12	< 0.001*
Time to reach deep block (min)	15.07 ± 2.70	10.77 ± 1.92	< 0.001*
Recovery Time (sec)	103.17 ± 16.27	96.83 ± 13.29	0.104

Data presented as Mean ± SD, *significant p value < 0.05; NMB= neuromuscular blockade

	Group R (n = 30)	Group RM (n = 30)	p value
Rescue fentanyl	7 (23.3)	0 (0)	0.011*
Intubating conditions			
Excellent	27 (90.0)	30 (100.0)	0.237
Good	3 (10.0)	0	

Data presented as n (%); *Significant as p value ≤ 0.05

acetylcholine presynaptic release.¹⁶ The current study results demonstrated that pre-treatment infusion of MgSO₄ 50 mg/kg added to low dose rocuronium 0.4 mg/kg was superior to rocuronium 0.6 mg/kg regarding onset of action, depth of neuromuscular block and depth of anesthesia with more hemodynamic stability in cancer larynx patients undergoing rigid/direct laryngoscopy procedures. Although, it is reported previously that

rocuronium action. Regarding the effect of MgSO₄ as an anesthetic adjuvant, we found that patients who received pre-treatment with MgSO₄ showed significant attenuation in hemodynamic response to intubation, clinically better intubating conditions and lower BIS values with faster onset to reach deeper level of anesthesia. MgSO₄ pretreatment can effectively improve intubating conditions when compared to other methods,

MgSO₄ augments muscle relaxation through its calcium antagonist effect without prolonging its duration of action.^{6,17} but our results demonstrated significant increase in block duration which is supported with other former studies.^{18,19} Choi and colleagues reported that adding MgSO₄ to low dose rocuronium resulted in augmented action and faster onset without prolonging neuromuscular block duration, such difference in duration of action with our results may be attributed to the difference in the dose of MgSO₄ they used being 30 mg/kg.⁶ Czarnetzki et al., used 60 mg/kg MgSO₄ added to rocuronium 0.6 mg/kg and stated that pre-treatment with MgSO₄ 15 min prior to induction of anesthesia while speeds the onset of NMB by 35 % but adversely prolongs its recovery time by 25%, although this is consistent with our results, but we demonstrated only 26% hastened onset and 15% increase in duration, such difference may be attributed to the higher doses of rocuronium and MgSO₄ they used.²⁰ On the other hand, Kussman and his colleagues reported that although pretreatment of rocuronium 0.6 mg/kg with MgSO₄ 60 mg/kg prolonged its duration of action, but it didn't hasten its onset, this might be explained by the timing of MgSO₄ administration being given only 1 min prior to the muscle relaxant.²¹ Thus, different doses of both rocuronium and MgSO₄ as well as the timing of MgSO₄ administration have an important role in modification of

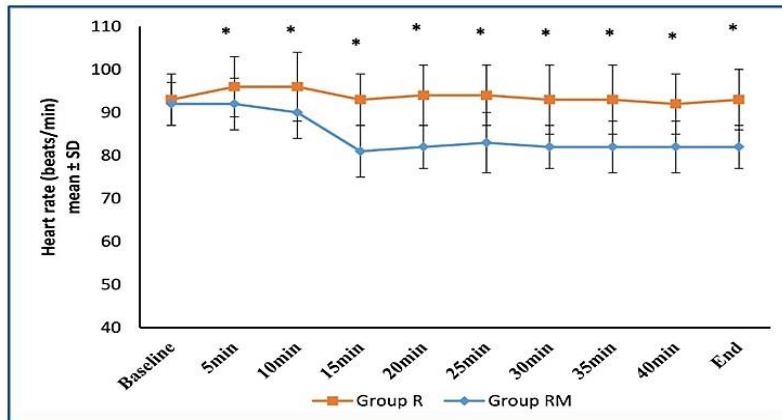


Figure 2: Comparison of mean heart rates (beats/min) in both groups

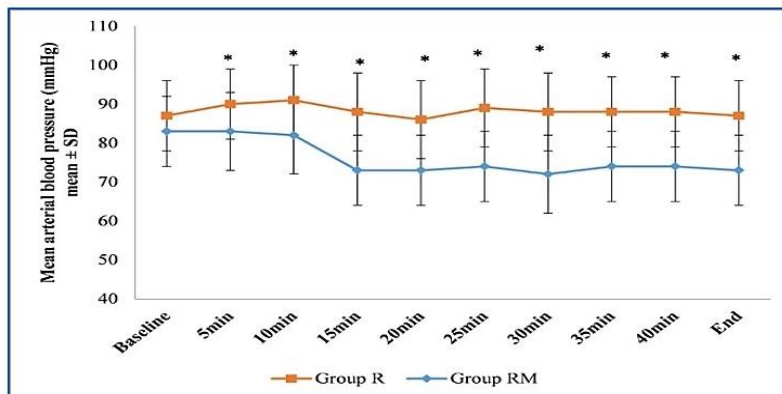


Figure 3: Comparison of mean arterial blood pressure (mmHg) in both groups

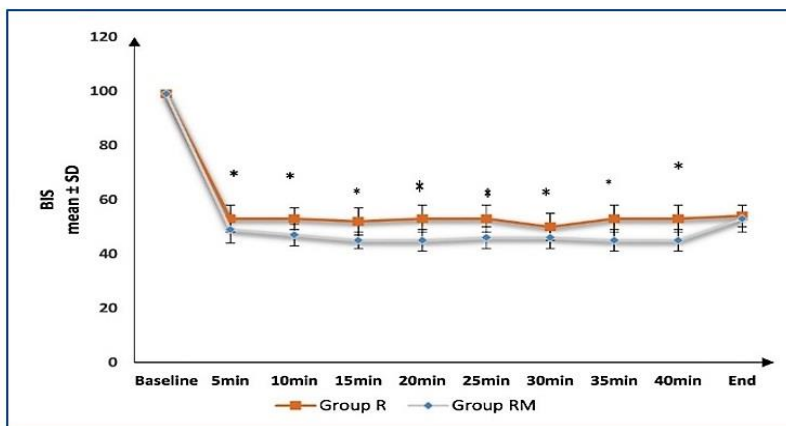


Figure 4: BIS in both groups.

it can be considered as a useful adjuvant to general anesthesia that helps in lower BIS values.^{8,22,23} This is consistent with the results reported by Amer et al., who stated that adding MgSO₄ resulted in significantly lower BIS values with less time to reach values below 60 in pediatric patients under general anesthesia.²⁴ MgSO₄ can

efficiently reduce intraoperative hemodynamics alteration, provides cardiovascular stability and attenuates the response to laryngoscopy and endotracheal intubation.^{8,25} Adding MgSO₄ 50 mg/kg to low dose rocuronium 0.4 mg/kg resulted in hastened onset of action with shorter time to achieve deep block but with prolonged duration of action which although not favored in short procedures but might be of benefit in longer ones. It had a favorable anesthetic profile when compared to conventional anesthesia.

5. Conclusion

Adding MgSO₄ to low dose rocuronium hastens the onset of rocuronium, shorten the time needed to achieve deep blockade with good intubating conditions and better intraoperative hemodynamic profile but showed prolonged duration of action when compared to standard dose rocuronium.

6. Limitations

Limitations to the current study included that we did not study adding same dose of magnesium to standard dose rocuronium. Also, we used inhalational anesthetics which might play a role in augmenting the effect of muscle relaxant used. Additionally, we used different doses of sugammadex for reversal of residual muscle relaxant according to depth of blockade, we think further studies on same dose of reversing drug might help in assessing the actual effect or mechanism of magnesium on depth of blockade and recovery time.

7. Conflict of interests

None declared by the authors.

8. Authors' contribution

All authors read and approved the final version of the manuscript

MW: Study idea, Patient recruitment, Interpretation and analysis of data

WE: Study idea, Patient recruitment, Interpretation and analysis of data, writing and editing the manuscript

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