■ ORIGINAL CLINICAL RESEARCH REPORT

Rapid Sequence Induction With a Standard Intubation Dose of Rocuronium After Magnesium Pretreatment Compared With Succinylcholine: A Randomized Clinical Trial

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BACKGROUND: Succinylcholine remains the muscle relaxant of choice for rapid sequence induction (RSI) but has many adverse effects. High-dose rocuronium bromide may be an alternative to succinylcholine for RSI but recovery times are nearly doubled compared with a standard intubating dose of rocuronium. Magnesium sulfate significantly shortens the onset time of a standard intubating dose of rocuronium. We set out to investigate whether intravenous (IV) pretreatment with $MgSO_4$ followed by a standard intubating dose of rocuronium achieved superior intubation conditions compared with succinylcholine.

METHODS: Adults were randomized to receive a 15-minute IV infusion of $MgSO_4$ (60 mg·kg^{-1}) immediately before RSI with propofol 2 mg·kg^{-1}, sufentanil 0.2 µg·kg^{-1} and rocuronium 0.6 mg·kg^{-1}, or a matching 15-minute IV infusion of saline immediately before an identical RSI, but with succinylcholine 1 mg·kg^{-1}. Primary end point was the rate of excellent intubating conditions 60 seconds after administration of the neuromuscular blocking agent and compared between groups using multivariable log-binomial regression model. Secondary end points were blood pressure and heart rate before induction, before and after intubation, and adverse events up to 24 hours postoperatively.

RESULTS: Among 280 randomized patients, intubating conditions could be analyzed in 259 (133 $MgSO_4$-rocuronium and 126 saline-succinylcholine). The rate of excellent intubating conditions was 46% with $MgSO_4$-rocuronium and 45% with saline-succinylcholine. The analysis adjusted for gender and center showed no superiority of $MgSO_4$-rocuronium compared with saline-succinylcholine (relative risk [RR] 1.06, 95% confidence interval [CI], 0.81-1.39, P = .659). The rate of excellent intubating conditions was higher in women (54% [70 of 130]) compared with men (37% [48 of 129]; adjusted RR 1.42, 95% CI, 1.07-1.91, P = .017). No significant difference between groups was observed for systolic and diastolic blood pressures. Mean heart rate was significantly higher in the $MgSO_4$-rocuronium group. The percentage of patients with at least 1 adverse event was lower with $MgSO_4$-rocuronium (11%) compared with saline-succinylcholine (28%) (RR 0.38, 95% CI, 0.22-0.66, P < .001). With saline-succinylcholine, adverse events consisted mainly of postoperative muscle pain (n = 26 [19%]) and signs of histamine release (n = 13 [9%]). With $MgSO_4$-rocuronium, few patients had pain on injection, nausea and vomiting, or skin rash during the $MgSO_4$-infusion (n = 5 [4%]).

CONCLUSIONS: IV pretreatment with $MgSO_4$ followed by a standard intubating dose of rocuronium did not provide superior intubation conditions to succinylcholine but had fewer adverse effects. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Does a combination of magnesium sulfate pretreatment followed by a standard intubating dose of rocuronium (0.6 mg·kg^{-1}) produce superior intubation conditions to succinylcholine?
- **Findings:** For rapid sequence induction, a combination of pretreatment with magnesium sulfate followed by a standard intubating dose of rocuronium does not provide superior intubating conditions compared with succinylcholine but has fewer adverse effects.
- **Meaning:** In view of our findings, we hypothesize that for rapid sequence induction, a combination of pretreatment with magnesium sulfate and a standard intubating dose of rocuronium might be an alternative to succinylcholine in circumstances where succinylcholine administration is not warranted.

Rapid sequence induction (RSI) is a frequently used procedure for endotracheal intubation in the emergency setting or in unfasted patients who are at risk of regurgitation. Succinylcholine remains the muscle relaxant of choice for RSI,[1,2] but it has many adverse effects.[3,4] There are alternatives that may be used instead of succinylcholine. For instance, with a high dose of rocuronium bromide, 1.0–1.2 mg·kg^{-1}, the same intubating conditions with a similar onset time as with succinylcholine may be achieved.[1,2] Also, pretreatment with intravenous (IV) magnesium may accelerate onset time of a nondepolarizing neuromuscular blocking agent.[5–7] The main problem with high dose nondepolarizing neuromuscular blocking agents is prolonged recovery time.[8] Today, this might not be perceived as a major problem as even deep, rocuronium-induced neuromuscular block can be antagonized with sugammadex.[9] But in many countries, sugammadex is not available or its use is restricted due to its high costs and strategies to reduce its usage are welcomed.[10] On the contrary, the role of magnesium in perioperative medicine is constantly increasing due to its analgesic and morphine sparing properties, neuroprotective features, and its potency to decrease overall anesthetic requirements.[11,12] This begs the question as to whether a standard intubating dose of, for instance, rocuronium, combined with magnesium, differs with regard to onset times and intubation conditions compared with succinylcholine. With a 15-minute IV infusion of magnesium sulfate 60 mg·kg^{-1} before a standard dose of rocuronium (0.6 mg·kg^{-1}), the onset time of the neuromuscular block was reduced by about 35% (from 120 to 72 seconds),

but recovery was only prolonged by 25%.[7] In addition, the interindividual variability in the onset of the neuromuscular blockade was lessened with this magnesium-rocuronium regimen, suggesting that the predictability of adequate intubating conditions was improved.[7] We designed a randomized controlled trial to compare a combination of magnesium with a standard intubating dose of rocuronium with succinylcholine in patients undergoing RSI. We chose a superiority trial design.

METHODS
Study Design
This randomized, double-blind, gender-stratified trial was conducted at 2 Swiss university hospitals (Geneva and Lausanne), following the recommendations of Good Clinical Research Practice in Neuromuscular Research.[13] The study protocol, patient information sheet, and informed consent form were approved by the ethics committees of Geneva University Hospitals (protocol no. CER11-235/NAC11-087) and Lausanne University Hospital (protocol no. 306/12), and by the Swiss Agency for Therapeutic Products (Swissmedic; 2012DR3098). The trial was registered before patient enrollment on clinicaltrials.gov (NCT01571908, principal investigator: Christoph Czarnetzki, date of registration: April 4, 2012). This article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Study Population and Recruitment
The anesthesia teams of Geneva and Lausanne University Hospitals identified eligible patients during the preanesthetic consultation and obtained written informed consent before enrollment. Included were male and female patients aged 18–65 years with an American Society of Anesthesiologists (ASA) physical status I or II and scheduled for elective surgery lasting longer than 60 minutes. Exclusion criteria were a history of allergy or hypersensitivity to rocuronium, succinylcholine, or MgSO$_4$; neuromuscular disease; history of malignant hyperthermia; preoperative medications known to influence neuromuscular function (eg, certain antibiotics [aminoglycosides], anticonvulsants [phenytoin]); electrolyte abnormalities (eg, hypermagnesemia or hyperkalemia); hepatic dysfunction (ie, bilirubin >1.5 × upper limit of normal [ULN], alanine aminotransferase [ALT] >2.5 × ULN,

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aspartate aminotransferase [AST] >2.5 × ULN); renal insufficiency (ie, creatinine >1.5 × ULN, creatinine clearance <60 mL·min^{-1} 1.73 m^{-2}, estimated by the formula of Cockroft & Gault); atrioventricular heart block; patients with magnesium treatment; those with a body mass index <19 or >28 kg·m^{-2}; pregnant or breastfeeding women; expected difficult intubation or mask ventilation; and patients having participated in any clinical trial within the previous 30 days.

Study Drug Preparation, Randomization, and Blinding

Each pharmacy of the 2 participating centers prepared study treatments and was responsible for randomization and maintenance of blinding in accordance with Good Manufacturing Practices. Randomization was stratified in a 1:1 ratio for gender due to a greater sensitivity to rocuronium in women.[14] Study drugs were taken from a commercial batch, and the number and expiry date of each batch were recorded. To ensure blinding, the treatments of the control group (saline-succinylcholine) and the experimental group (magnesium-rocuronium) were matched (100-mL infusion bags containing 0.9% saline or MgSO$_4$ 60 mg·mL^{-1} and 10-mL syringes containing succinylcholine 16.6 mg·mL^{-1} or rocuronium 10 mg·mL^{-1}). Study drugs were prepared and randomized 24 hours in advance and delivered in sealed plastic bags identified by a randomization number, name and number of the study, expiry date, mode of administration (IV), and storage condition.

In a previous study, the infusion of MgSO$_4$ in awake patients was often accompanied by a sensation of flush or slight heat in the arm where the perfusion was positioned.[7] Also, the administration of succinylcholine may be associated with the occurrence of fasciculations.[15] We therefore anticipated that adequate blinding of the treatments would be difficult. Several precautions were taken to minimize observer bias. First, patients were not asked actively by the investigators about any symptoms related to the IV pretreatment, but patients could report spontaneously on symptoms and complaints. Second, an anesthesiologist and a nurse anesthetist were responsible for the administration of all drugs during induction and were in charge of the patient throughout the surgical procedure, but they were not involved in the intubating procedure and scoring of intubating conditions. Third, a second anesthesiologist blinded to study drug administration, intubated the patient, and scored intubating conditions. This second, independent, anesthesiologist entered the preparation room only on call and only once the patient was ready to be intubated (ie, not earlier than 45 seconds after injection of the neuromuscular blocking agent). Finally, no more than 2 intubating anesthesiologists per center participated in the study to limit interobserver variability.

Study Drug Administration

In the experimental group, patients received 1 mL·kg^{-1} of the MgSO$_4$ solution as a pretreatment, which corresponded to 60 mg·kg^{-1} of MgSO$_4$. In the control group, patients received a matching 1 mL·kg^{-1} infusion containing physiological saline (0.9% NaCl). Pretreatments were administered during 15 minutes using a volumetric infusion pump (Infusomat, Braun Medical SA, Sempach, Switzerland). Once the pretreatment was finished, anesthesia was induced (see Induction and Intubation) and 0.06 mL·kg^{-1} of the neuromuscular blocking agent was administered using the matching 10-mL syringe. This regimen ensured that patients in the experimental group received rocuronium 0.6 mg·kg^{-1} and those in the control group received succinylcholine 1 mg·kg^{-1}.

Induction and Intubation

The anesthesiologist in charge of the patient was free to administer oral midazolam as a premedication at last 1 hour before induction of anesthesia or IV midazolam in the preparation room. Standard noninvasive monitoring included acceleromyography with a TOF Watch SX monitor (Organon, Oss, the Netherlands). For induction, patients were installed with the head slightly raised (sniffing position). Preoxygenation via a facemask was begun, and IV sufentanil 0.2 µg·kg^{-1} was given. Anesthesia was induced 3 minutes later using IV propofol 2 mg·kg^{-1}. On loss of consciousness, patients received the neuromuscular blocking agent according to randomization. Patients were not ventilated before orotracheal intubation. No cricoid pressure was exerted. The procedure of intubation was standardized. The time point of injection of the neuromuscular blocking agent was defined as time 0. At time 45 seconds, the intubating anesthesiologist entered the room, approached the head of the patient, started direct laryngoscopy at time 50 seconds, and intubated the trachea at time 60 seconds. All intubating anesthesiologists were experienced consultants.

Study End Points

The primary end point was the percentage of patients with excellent intubating conditions. Intubating conditions were graded as excellent, good, or poor using a modified scale according to the recommendations of Good Clinical Research Practice in Neuromuscular Research (Table 1).[13] Scoring was based on ease of laryngoscopy, the position of the vocal cords, and the patient's reactions to the insertion of the endotracheal tube. In addition to these qualifiers, we added the outcome "intubating failure," defined as a not completed orotracheal intubation within 30 seconds after the start of direct laryngoscopy (ie, 80 seconds after injection of the neuromuscular blocking agent). In the case of intubating failure, the usual guidelines for a "can ventilate – cannot intubate" situation were followed.

Table 1. Intubating Conditions According to Good Clinical Practice in Neuromuscular Research

Evaluation of intubating conditions[a]

Variable assessed	Clinically acceptable		Not clinically acceptable
	Excellent	Good	Poor
Laryngoscopy[b]	Easy	Fair	Difficult
Vocal cords position	Abducted	Intermediate/moving	Closed
Reaction to insertion of the tracheal tube and cuff inflation (diaphragmatic movement/coughing)	None	Slight[c]	Vigorous/sustained[d]

According to Fuchs-Buder et al.[13]

[a]Intubation conditions: excellent (all qualities are excellent); good (all qualities are either excellent or good); and poor (the presence of a single quality listed under "poor").

[b]Laryngoscopy: easy (jaw relaxed, no resistance to blade insertion); fair (jaw not fully relaxed, slight resistance to blade insertion); and difficult (poor jaw relaxation, active resistance of the patient to laryngoscopy).

[c]One to 2 weak contractions and/or movement for <5 s.

[d]More than 2 contractions and/or movement for longer than 5 s.

The intubating anesthesiologist rated the various variables describing intubating conditions and their quality immediately after orotracheal intubation. Patients with a Cormack & Lehane grade of 3 or 4 were excluded from the analysis of the primary end point as with these grades, the position of the vocal cords cannot be assessed.[16] However, these patients were considered for the analysis of adverse events.

Secondary end points were heart rate and systolic and diastolic blood pressure immediately before intubation, and at 1 and 5 minutes after intubation. Safety evaluation consisted of spontaneously reported symptoms and complaints during the infusion of the pretreatment (nausea/retching, skin rash, pain at injection) and the appearance of signs of histamine release (bronchospasm, erythema, edema, hypotension) after the injection of the neuromuscular blocking agent. Arterial hypotension was defined as a decrease in mean arterial pressure of >40%. At the postanesthetic visit, the day after the intervention, patients were screened for intraoperative awareness, muscle pain, and for any minor or major adverse event.

Statistical Analysis

Demographic characteristics were described as numbers of patients and percentages for qualitative data and as means and standard deviations for quantitative data. Intubating conditions were described as numbers of patients and percentages, and hemodynamic measurements as means and standard deviations. All data were described overall and by group of randomization. Due to the stratified randomization, the comparison of excellent intubating conditions between groups was performed using a log-binomial regression model adjusting for gender and center (and no interaction term). Similarly, between-group differences on secondary end points were assessed using linear regression models adjusting for gender and center. For the 3 variables of intubating conditions, both groups were compared using χ^2 test. The saline-succinylcholine group was used as a reference group for the calculation of relative risk.

The rate of excellent intubating conditions between groups stratified by gender, and by gender and center, were also compared using χ^2 test. In addition to the stratified analyses, we estimated interaction terms to test the differences in effects between subgroups of patients. Subgroup analyses should be regarded as explorative only since they were not described in the study protocol and they have low statistical power.

Two-sided $P < .05$ were considered significant for all analyses. There was no adjustment of P values to account for multiple comparisons. Analyses were performed using R software (Vienna, Austria; http://www.R-project.org).[17]

Sample Size Determination

This trial was designed as a superiority study. We tested the hypothesis that for RSI, a combination of magnesium with a standard intubating dose of rocuronium was superior to succinylcholine. Sample size was calculated by taking the level of statistical significance as $\alpha = .05$ (2-sided) and $\beta = .1$. To test the primary hypothesis that the rate of excellent intubating conditions was higher (80%) with magnesium-rocuronium compared with succinylcholine (60%),[18] we needed 110 patients in each group. We intended to randomize 2 times 140 patients in each group to allow for dropouts. The total number of patients necessary for inclusion was therefore 280.

RESULTS

Participant Flow

In total, 280 patients were randomized between September 20, 2012, and July 9, 2015 (magnesium-rocuronium [141 patients]; saline-succinylcholine [139 patients]) (Figure). In 21 patients (magnesium-rocuronium [8 patients]; saline-succinylcholine [13 patients]), the primary end point could not be analyzed for various reasons (Figure). Eventually, 259
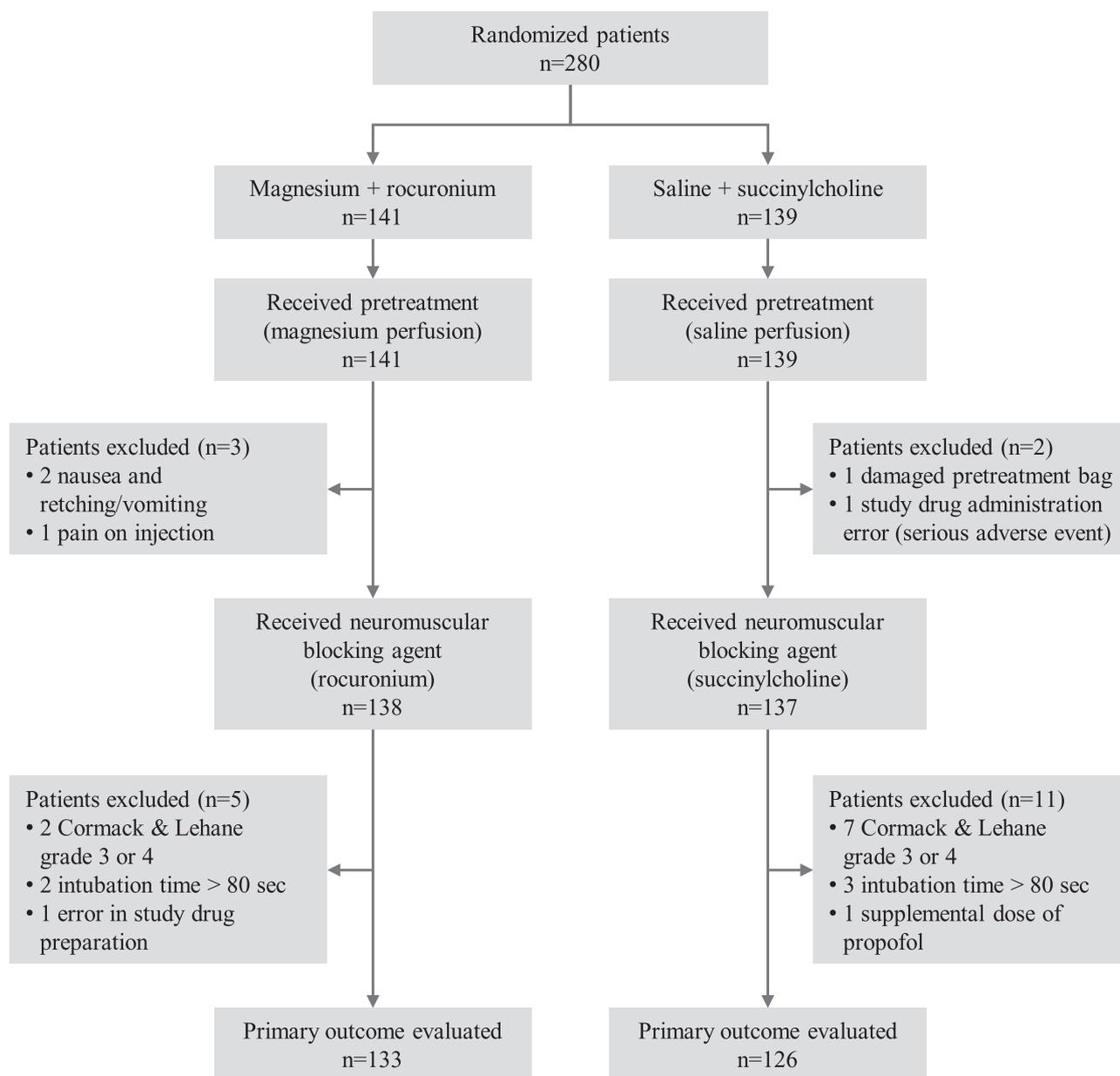
Figure. Study flowchart.

patients (magnesium-rocuronium [133 patients]; saline-succinylcholine [126 patients]) were included in the primary end point analysis.

Characteristics of the Study Population

The demographic characteristics of both groups were similar (Table 2); 50% of patients were women.

Primary End Point: Evaluation of Intubating Conditions

No significant difference was observed in the percentage of excellent intubating conditions between both groups (magnesium-rocuronium 46% [61 of 133]; saline-succinylcholine 45% [57 of 126]), although ease of laryngoscopy was more often

graded excellent with magnesium-rocuronium (Table 3). Multivariable analysis adjusted for gender and center showed no superiority of magnesium-rocuronium on the rate of excellent intubating conditions (relative risk [RR] for magnesium-rocuronium compared with saline-succinylcholine 1.06; 95% confidence interval [CI], 0.81-1.39; $P = .659$) (Table 4). The overall rate of excellent intubating conditions was higher in women (54% [70 of 130]) compared with men (37% [48 of 129]; adjusted RR 1.42; 95% CI, 1.07-1.91; $P = .017$).

Posthoc Subgroup Analyses

Impact of Gender. In men, the rate of excellent intubating conditions was 30% (20 of 66) in the magnesium-rocuronium

Table 2. Demographics and Baseline Characteristics of 259 Patients Included in the Efficacy Analyses

	N = 259	Mag-Roc (N = 133)	Sal-Succ (N = 126)
Gender (women), n (%)	130 (50)	67 (50)	63 (50)
Age, y (mean ± SD)	41.6 ± 12.1	41.9 ± 11.7	41.3 ± 12.5
Weight, kg (mean ± SD)	69.9 ± 10.5	70.2 ± 11	69.5 ± 9.9
Height, cm (mean ± SD)	171.2 ± 9.6	171.1 ± 9.9	171.3 ± 9.3
BMI, kg·m^{-2} (mean ± SD)	23.8 ± 2.3	23.9 ± 2.3	23.6 ± 2.3
Midazolam orally, n (%)	64 (25)	32 (24)	32 (25)
Midazolam IV, n (%)	77 (30)	38 (29)	39 (31)
Midazolam orally, and/or IV, n (%)	135[a] (52)	66 (50)	69 (55)

Abbreviations: BMI, body mass index; IV, intravenous; Mag-Roc, magnesium (pretreatment) + rocuronium; Sal-Succ, saline (pretreatment) + succinylcholine; SD, standard deviation.

[a]Six patients received midazolam orally, and IV.

Table 3. Variables of Intubating Conditions According to Study Treatment (N = 259)

	n = 259 (%)	Mag-Roc (n = 133) (%)	Sal-Succ (n = 126) (%)	P value[a]
Intubating conditions				
Excellent	118 (46)	61 (46)	57 (45)	.863
Good	97 (37)	51 (38)	46 (37)	
Poor	44 (17)	21 (16)	23 (18)	
Ease of laryngoscopy				
Excellent	236 (91)	127 (95)	109 (87)	.016
Good	21 (8)	5 (4)	16 (13)	
Poor	2 (1)	1 (1)	1 (1)	
Vocal cords' position				
Excellent	233 (90)	117 (88)	116 (92)	.374
Good	26 (10)	16 (12)	10 (8)	
Reaction to insertion of the tracheal tube				
Excellent	134 (52)	68 (51)	66 (52)	.768
Good	83 (32)	45 (34)	38 (30)	
Poor	42 (16)	20 (15)	22 (17)	

Abbreviations: Mag-Roc, magnesium (pretreatment) + rocuronium; Sal-Succ, saline (pretreatment) + succinylcholine.

[a]Chi-square test.

Table 4. Primary End Point: Excellent Intubating Conditions

Variable	Modality	Excellent intubating conditions, n (%)	Adjusted RR	95% CI	P value[a]
Treatment	Mag-Roc (N = 133)	61 (46)	1.06	0.81-1.39	.659
	Sal-Succ (N = 126)	57 (45)	1		
Gender	Men (N = 129)	48 (37)	1		
	Women (N = 130)	70 (54)	1.42	1.07-1.91	.017
Center	B (N = 150)	74 (49)	1		
	A (N = 109)	44 (40)	0.91	0.67-1.20	.502

Multivariable analysis adjusted for treatment, gender, and center (N = 259).

Abbreviations: CI, confidence interval; Mag-Roc, magnesium (pretreatment) + rocuronium; RR, relative risk; Sal-Succ, saline (pretreatment) + succinylcholine.

[a]Log-binomial regression model adjusting for gender and center.

group and was 44% (28 of 63) in the saline-succinylcholine group (P = .139). In women, the rate of excellent intubating conditions was 61% (41 of 67) in the magnesium-rocuronium group and was 46% (29 of 63) in the saline-succinylcholine group (P = .120). The treatment effect was significantly different in men and women (interaction term, P = .019) with a higher rate of excellent intubating conditions with magnesium-rocuronium in women than in men. Stratified analyses by gender and center showed a similar tendency. In 1 center, the difference in the rate of excellent intubating conditions in men was significantly lower in the magnesium-rocuronium group (22% [6 of 27] compared with the saline-succinylcholine group (55% [16 of 29]) (P = .025) (Table 5).

Impact of Midazolam. Patients having received oral or IV midazolam (N = 135) had a better rate of excellent intubating conditions than those having not received midazolam (N = 124) (53% [71 of 135] vs 38% [47 of 124]), but without between-treatment group difference (52% [34 of 66] in the magnesium-rocuronium group and 54% [37 of 69] in the saline-succinylcholine group for patients having received midazolam versus 40% [27 of 67] and 35% [20 of 57], respectively, for patients having not received midazolam).

Secondary End Points. There was no significant difference between groups in systolic and diastolic blood pressure at any time point (Supplemental Digital Content 1, Table 1,

Table 5. Exploratory Subgroup Analyses Stratified by Gender and Center

		Mag-Roc	Sal-Succ	P value[a]
Overall (n)	259	133	126	
Men (n)	129	66	63	
Excellent intubating conditions	48 (37%)	20 (30%)	28 (44%)	.139
Women (n)	130	67	63	
Excellent intubating conditions	70 (54%)	41 (61%)	29 (46%)	.120
		Mag-Roc	Sal-Succ	P value[a]
Center A (n)	109	58	51	
Men (n)	73	39	34	
Excellent intubating conditions	26 (36%)	14 (36%)	12 (35%)	1
Women (n)	36	19	17	
Excellent intubating conditions	18 (50%)	11 (58%)	7 (41%)	.504
		Mag-Roc	Sal-Succ	P value[a]
Center B (n)	150	75	75	
Men (n)	56	27	29	
Excellent intubating conditions	22 (39%)	6 (22%)	16 (55%)	.025
Women (n)	94	48	46	
Excellent intubating conditions	52 (55%)	30 (63%)	22 (48%)	.221

Abbreviations: Mag-Roc, magnesium (pretreatment) + rocuronium; Sal-Succ, saline (pretreatment) + succinylcholine.
[a]Chi-square test.

http://links.lww.com/AA/D290). The mean heart rate was significantly higher in the magnesium-rocuronium group by approximately 5 beats per minute at each time point.

Safety Evaluation. Among the 280 randomized patients, 54 (19%) presented at least 1 adverse event (Supplemental Digital Content 2, Table 2, http://links.lww.com/AA/D291). The percentage of patients with at least 1 adverse event was almost 3 times lower with magnesium-rocuronium (11% [15 of 141]) compared with saline-succinylcholine (28% [39 of 139]) (RR 0.38, 95% CI, 0.22-0.66, $P < .001$). Five patients had symptoms related to the perfusion of the study pretreatment (all in the magnesium-rocuronium group [4%]): 3 had nausea or retching or vomiting (2 wished to discontinue the study); 1 patient had an erythema at the injection site; and 1 had pain at the injection site (wished to discontinue the study). Data of all 3 patients who wished to discontinue the study were excluded from the analysis of the primary end point but were included into the safety analyses.

Eighteen of the remaining 275 patients (7%) presented symptoms that may be attributed to the injection of the neuromuscular blocking agent: 5 of 138 (4%) in the magnesium-rocuronium group and 13 of 137 (9%) in the saline-succinylcholine group. One case of bronchospasm of mild intensity that did not require treatment was observed in the saline-succinylcholine group. One episode of arterial hypotension was reported in each study group. Arterial hypotension was easily treated with vasopressors. No patient presented an edema of mucosa or skin due to histamine release.

The most frequently reported adverse event at the 24-hour postoperative visit was muscular pain (10%), mainly in patients who had received succinylcholine (19% vs 1%, respectively, $P < .001$). With the exception of 1 patient who had moderate pain, symptoms

were mild; no patient needed treatment. There were 7 reports of minor adverse events, considered unrelated to study treatments, and equally distributed between the 2 groups. They were mild or moderate and resolved uneventfully.

Two serious adverse events were identified during the study period. In 1 patient in the control group, the content of the syringe with succinylcholine was accidentally injected into the pretreatment perfusion bag and the infusion was commenced. As soon as the patient complained of muscle weakness, the error was discovered and anesthesia was induced. Anesthesia and surgery were uneventful. Postoperatively, the patient had a psychological evaluation and assistance, and follow-up was uneventful. One patient in the experimental group had to be reoperated due to postoperative hemorrhagic shock. The patient fully recovered and this event was considered to be unrelated to the study treatment.

DISCUSSION

Our study showed no superiority of a combination of $MgSO_4$ 60 mg·kg^{-1} and rocuronium 0.6 mg·kg^{-1} compared with succinylcholine 1 mg·kg^{-1} on the rate of excellent intubating conditions during RSI in adult patients. There were more adverse events with succinylcholine, mainly muscle pain and symptoms that may be attributed to histamine release. Overall, the rate of excellent intubating conditions was statistically higher in women. This was primarily due to the higher rate of women with excellent intubating conditions who received magnesium-rocuronium. Due to small sample sizes in the subgroup analyses, statistical power to detect clinically meaningful differences was insufficient.

Magnesium has a direct impact on neuromuscular transmission by decreasing the calcium influx and reducing the amount of acetylcholine released.[19–21] After pretreatment with IV $MgSO_4$, a reduction in the onset time was observed with atracurium, vecuronium, and rocuronium.[5–7] Several studies have tested the effect of various magnesium-rocuronium combinations on intubating conditions.[22–24] Kim et al[23] and Park et al[24] compared a combination of $MgSO_4$ 50 mg·kg^{-1} and rocuronium 0.6 mg·kg^{-1} with rocuronium 0.9 mg·kg^{-1}. They did not include a control group receiving succinylcholine, the gold standard for RSI. We found no studies in the literature comparing $MgSO_4$ 60 mg·kg^{-1} and a standard intubating dose of rocuronium 0.6 mg·kg^{-1} with succinylcholine 1 mg·kg^{-1}. One study compared succinylcholine 1 mg·kg^{-1} with high-dose rocuronium (1.2 mg·kg^{-1}) and a combination of magnesium and high-dose rocuronium.[22] Results of this study must be interpreted with caution as only 20 patients were included in each arm and the authors did not describe how intubation conditions

were evaluated.[22] They concluded that the magnesium-rocuronium combination significantly shortened the onset time of the neuromuscular block and significantly improved intubating conditions compared with high-dose rocuronium alone. Similar to our study, the combination of magnesium and high-dose rocuronium provided comparable intubating conditions to that of succinylcholine.

Combining magnesium with a standard intubation dose of rocuronium (0.6 mg·kg^{-1}), instead of using high-dose rocuronium (1.2 mg·kg^{-1}) alone, may be a more useful regimen for RSI as the duration of the neuromuscular block was prolonged by 25% only when magnesium was combined with rocuronium, compared with rocuronium alone,[7] while the recovery time with high-dose rocuronium was nearly doubled.[8] Magnesium in doses similar to our regimen is routinely used in anesthesia due to its analgesic and morphine sparing properties.[11,12] It is also used as part of opioid-free anesthesia.[25,26] Usual magnesium regimens often include a loading dose similar to ours (40–60 mg·kg^{-1}) which can be easily anticipated before anesthesia induction while the patient is monitored and prepared for anesthesia. Few emergency patients requiring RSI for full stomach may need immediate intubation and even then there is often sufficient time to administer drugs before induction, such as gastric prokinetic agents.[27]

Omitting high doses of rocuronium may allow to await spontaneous recovery of the neuromuscular block and avoid expensive antagonization with sugammadex under the premise that objective neuromuscular monitoring is available (documentation of train of four [TOF] ratio ≥ 0.9), which is the only method of assuring satisfactory recovery of neuromuscular function.[28] If reversal is needed in patients with a magnesium pretreatment, the efficacy of recommended doses of sugammadex for the reversal of a moderate or deep neuromuscular block is not diminished.[29]

Less than 50% of our patients had excellent intubating conditions with both experimental and control treatment. These rates were low compared with the literature. In the studies by Naguib et al, excellent intubating conditions were found in 63% and 80% of patients with succinylcholine 1 mg·kg^{-1}.[18,30] Kim et al[23] reported on excellent intubating conditions in nearly 80% of patients who had received MgSO$_4$ 50 mg·kg^{-1} and rocuronium 0.6 mg·kg^{-1}. However, none of these studies compared a magnesium 60 mg·kg^{-1}-rocuronium 0.6 mg·kg^{-1} combination with succinylcholine 1 mg·kg^{-1}. It remains unclear why our rates of excellent intubating conditions were relatively low. The induction and intubation protocols were strictly standardized. Several measures such as matching of treatments, anonymous delivery of treatments, no systematic reporting of symptoms related to the IV pretreatment by patients, intervention of 2 anesthesiologists (1 for the administration of drugs during induction and the follow-up of the patient during the surgical procedure, and the second for the intubation and the scoring of intubation conditions), and no more than 2 intubating anesthesiologists per center, were adopted to minimize observer bias and to maintain proper blinding of treatments. All observers were experienced anesthesiologists. Also, group sizes were much larger than in previous similar studies.[18,22,23,24,30]

There was an imbalance between groups in the number of patients who could not be included into the primary analysis since intubation was not completed within 80 seconds after injection of the study drugs or the patients had a Cormack-Lehane grade 3 or 4. The number of these dropouts was higher in the control group. We may speculate that inclusion of these patients into the analyses would have led to a more conservative estimate of treatment differences, and thus a larger difference between the intervention and control groups.

Nineteen percent of patients had at least 1 adverse event and almost three-quarters of those had received succinylcholine. The most commonly reported succinylcholine-related adverse event was muscle pain. Succinylcholine-related muscle ache is common and it may not necessarily be regarded as a true medical problem as it is self-limiting, never becomes chronic, and responds favorably to nonsteroidal anti-inflammatory drugs.[15] Adverse effects during the injection of the neuromuscular blocking agent were also more frequent in the succinylcholine group; most of these patients had erythema. All observed manifestations were mild to moderate and did not require treatment. Five patients had symptoms related to the pretreatment with IV MgSO$_4$ such as pain at the site of injection, skin rash, or nausea and vomiting. Three of those patients wished to terminate the study and were excluded from the analysis of the primary end point. Clinicians who choose a magnesium-rocuronium combination for RSI must be aware that such adverse events may occur in about 1%–8% of patients (5 of 141, Clopper-Pearson 95% CI, 1.2-8.1). In general, adverse effects related to a preoperative magnesium infusion are well tolerated.[6,7,29] Two adverse events that were classified as serious were identified during the study. One was related to the accidental administration of the neuromuscular blocking agent in an awake patient. The other was not related to study treatment. No significant difference between groups was shown for values of systolic and diastolic blood pressure before induction, and before and after intubation. There was on average a significantly higher heart rate in the magnesium-rocuronium group compared with the succinylcholine group. This may be attributed to a decrease in peripheral vascular resistance through a magnesium-mediated vasodilator effect.[31] It has been suggested that MgSO$_4$ improves

hemodynamic stability during orotracheal intubation through a vasodilator effect related to reduced catecholaminergic release and calcium channel block.[31]

Overall, the rate of excellent intubating conditions was significantly higher in women. This was related to a higher rate of women who had excellent intubating conditions after having received magnesium-rocuronium. This result, although not the primary interest of our study, was not unexpected as it is well known that there is an impact of gender on the action of nondepolarizing neuromuscular blocking agents. Adamus et al[14] have shown an increased susceptibility of aminosteroidal blockers such as rocuronium in women.[32,33] In these studies, the delay in the installation of the neuromuscular block was shortened, while the duration of the block was prolonged in women compared with men. Our observations may be regarded as an opportunity to define a research agenda to further study gender differences in pharmacology. Future trials may test the hypothesis that a magnesium-rocuronium combination has a more pronounced effect in women than in men.

Post hoc subgroup analyses also suggested an improvement in intubating conditions in patients receiving midazolam. Midazolam has muscle relaxant properties via α2 γ-aminobutyric acid A (GABAA) receptors.[34–36] Additionally, anxiolytic properties of midazolam may reduce basal tone in airway muscles.[37] Midazolam also potentiates the effects of opioids and propofol.[38–40] When used as a premedication, midazolam has shown improved conditions of facial mask ventilation and insertion of a laryngeal mask.[36,41] However, no data has so far identified a benefit of midazolam, alone or in combination with other drugs, on intubating conditions. It may be assumed that the improvement in intubating conditions after premedication with midazolam was caused by muscle relaxant effects and synergy with anesthetic induction agents.

CONCLUSIONS

We designed this trial as a superiority study. Therefore, the methodologically correct interpretation of the data must be that for RSI, a combination of IV magnesium pretreatment 60 mg·kg⁻¹ followed by a standard intubating dose of rocuronium (0.6 mg·kg⁻¹) does not provide superior intubating conditions compared with succinylcholine 1 mg·kg⁻¹, but might be an alternative to succinylcholine in circumstances where succinylcholine administration is not warranted. A randomized study with a noninferiority design and with a larger cohort should be carried out to investigate whether a magnesium-rocuronium combination provides intubation conditions that are not inferior to succinylcholine. Furthermore, a gender effect should be investigated. ■

DISCLOSURES
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