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# The Effect of Saline Flush After Rocuronium Bolus on Intubating Conditions in Adult Patients Undergoing Elective Surgery: A Randomized Controlled Trial

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**Abstract:** Background: In emergency surgeries requiring endotracheal intubation, the time to effect of neuromuscular blocking drugs is a crucial time to avoid hypoxia and aspiration into the lungs. Various strategies have been undertaken to shorten this time. All these methods have positive results but some are associated with side effects. The effectiveness of a muscle relaxant can either be assessed using the train of four or intubating conditions on the Goldberg scale. In this study, we investigated the effects of a 20 ml saline bolus following intravenous rocuronium at 0.6 mg/kg on the proportions of patients with excellent intubating conditions at one minute. Methodology: Fifty-two patients were randomly allocated to the saline bolus group or the no saline flush group. Anaesthesia was induced using propofol and remifentanyl via target-controlled infusion (TCI) and maintained with the same. Rocuronium 0.6 mg/kg intravenous (IV) was administered followed by a 20 ml saline flush in the study group compared to administration of 0.6 mg/kg rocuronium without a saline bolus in the control group. Intubation conditions were assessed using the Goldberg scale filled by the intubating doctor. The onset of neuromuscular block was assessed by the train of four T1 height depression with an accelerometer attached to the adductor pollicis muscle. Results: There were 25 patients in each group. Patients in both groups were comparable with respect to demographic profiles. In the group with a flush, 18 (62.1%) patients had “excellent” and seven (33.3%) patients had “good” intubating conditions as opposed to 11 (37.9%) having “excellent” and 14 (66.7%) having “good” intubating condition in the group without a flush. The distribution of intubating conditions for the two groups showed a difference of 24.2% in the proportion of patients with excellent intubating conditions which was statistically significant ( $P=0.042$ ). There was no association between twitch height at one minute and intubating conditions. Conclusion: In this group of patients studied, the administration of a 20 ml saline flush after 0.6mg/kg rocuronium significantly increases the proportion of patients with excellent intubating conditions as compared to rocuronium without a saline flush.

**Keywords:** Intubating Conditions, Rocuronium, Saline Flush, General Anaesthesia, Adult Patients

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## 1. Introduction

Endotracheal intubation is a medical procedure in which a tube is placed into the trachea through the mouth or nose. In emergencies, the endotracheal tube is placed using a technique referred to as rapid sequence intubation (RSI). Muscle relaxants are one of the medications used to aid this process [1].

The onset time of neuromuscular blockade is a time where

patients are predisposed to hypoxia and aspiration into the lungs. For these reasons, muscle relaxants with a rapid onset are used. The adequacy of muscle paralysis is monitored by acceleromyography or using the Goldberg scale that assesses intubating conditions [2-5].

Suxamethonium, a depolarizing muscle relaxant, has been the gold standard for a long time. However, it has numerous unwanted effects and several contraindications which are mostly unknown at the time a patient requires intubation in

an emergency setting [6].

Rocuronium, a non-depolarizing muscle relaxant has been studied as an alternative to suxamethonium for muscle paralysis in patients requiring emergency intubation. It possesses a better safety profile and even though it has a longer duration of action, it has a known reversal agent, sugammadex [7, 8].

Intubating conditions resulting from suxamethonium compared to rocuronium administration during emergency intubations have been studied widely with results showing suxamethonium to be slightly superior to rocuronium. Rocuronium is used more commonly in different places such as the emergency department and critical care unit though not free of reported anaphylactic reactions [9-12].

Despite rocuronium being a viable alternative, concerns have arisen due to its inferior intubating conditions when compared to suxamethonium. Several interventions have been studied in an attempt to improve onset of action of rocuronium in order to improve the intubating conditions; these include: using higher doses of rocuronium, increasing patients cardiac output (ephedrine/ phenylephrine pre-treatment before rocuronium), administering drug via central circulation (use of central venous access), priming with rocuronium (rocuronium given before hypnotic agent), drug admixture (rocuronium mixed with mivacurium) or use of a flush [13-17].

The aim of our study was to compare the effect of adding 20 ml saline flush after intravenous administration of 0.6 milligrams per kilogram of rocuronium on the proportions of patients with excellent intubating conditions at one minute. Our primary objective was to determine the effect of a 20ml saline flush after 0.6 milligrams per kilogram intravenous rocuronium on the proportion of patients with excellent intubating conditions at one minute assessed by the Goldberg scale in adult patients undergoing elective surgery under general anaesthesia. Our secondary objectives were to determine the relationship between intubating conditions and the twitch height at one minute following a saline flush with 0.6 milligrams per kilogram intravenous Rocuronium in patients having elective surgery under general anaesthesia with oral endotracheal intubation, and to determine the effect of saline flush after 0.6 milligrams per kilogram intravenous Rocuronium on the onset time of Rocuronium as measured by the degree of twitch height depression in adult patients undergoing elective surgery under general anaesthesia.

We hypothesized that a 20ml saline flush following 0.6 milligrams per kilogram intravenous rocuronium does not increase the proportion of patients with excellent intubating conditions at one minute in adult patients undergoing elective surgery under general anaesthesia.

We studied patients coming for elective surgery, with normal airway examination, belonging to ASA categories I-III, and having total intravenous anaesthetic to enable demonstration of effect before it can be studied in emergency cases.

## 2. Materials and Methods

The study was carried out between November 2018 and November 2019. Participant flow diagram is shown in figure 1 below. This was a randomized controlled trial. This study was conducted at Aga Khan University Hospital-Nairobi.

The target population was adult patients coming for surgery under general anaesthesia and require oral endotracheal intubation. The sample population included patients in all ASA categories, between 18 and 65 years scheduled for surgery electively under general anaesthesia and scheduled to undergo oral endotracheal intubation at the Aga Khan University Hospital- Nairobi.

We included all ASA grade I to III patients in our study who:

1. Were between 18-65 years scheduled for non-emergent surgery under general anaesthesia requiring oral endotracheal intubation. The cut off of 18years was determined based on the laws of Kenya age of majority act chapter 33. On the other hand, 65-year cut-off was decided based on possible confounders to the outcome of the study. This includes but not limited to arthritic changes in the cervical spine, being edentulous and dental degeneration.
2. Were scheduled for surgery between 8 a.m. and 6 p.m. (This is the time when elective cases are scheduled in the study institution).
3. Were willing to give voluntary and informed consent to be eligible to participate in the study.
4. The anaesthetic technique included total intravenous anaesthesia (TIVA).

Reasons for exclusion from the study were:

1. Patients who declined to consent participation in the study.
2. Patients known to have an allergy to rocuronium or any other of the study drugs.
3. Patients scheduled for emergency surgery.
4. Patients with ASA category IV to VI.
5. Patients known to have a difficult airway (from previous anaesthetic notes or history) or suspected to have a difficult airway using the modified LEMON criteria score (including a body mass index (BMI) above 35kg/m<sup>2</sup>) during the anaesthesia review [18].
6. Patients who had non-emergency surgery scheduled between 6 p.m. and 8 a.m.
7. Patients with heart failure or chronic liver disease and expectant mothers.

Generally, emergent intubations are done after visible fasciculation for suxamethonium (usually at 30- 45 seconds) and at one-minute following an appropriate dose of rocuronium [19]. One of the ways to assess ease of intubation is using the Goldberg scale of intubating conditions [5]. These intubating conditions are graded as excellent-, good- and poor-intubating conditions based on particular parameters observed at the time of intubation. In this study, participants were grouped into these three categories and proportions in each category presented in table form. This is

shown in table 1 below. Prior studies have shown suxamethonium to have better proportions of patients in the excellent intubating conditions category (compared to rocuronium). One minute in the case of an emergency intubation is a long time, improving the onset of a muscle relaxant by even 30 seconds is clinically relevant as this could reduce the risk of adverse outcomes such as aspiration and hypoxia.

This sample size calculation was based on the difference in proportions of excellent intubation between the saline flush group and the no saline flush group (for a randomized control superiority trial for dichotomous variable) [20].

This calculation was based on a previous trial by Mencke T et al who compared the intubating conditions provided by rocuronium as opposed to suxamethonium. Suxamethonium had 57% of patients with excellent intubating conditions and rocuronium had 21%. This represented a 36% difference in the proportion of patients with excellent intubating conditions [21]. This study was picked since it compared intubating conditions between Suxamethonium and the rocuronium in a fashion more comparable to this study's methodology.

Comparison of two proportions was the primary objective was used to determine the required sample size. With a 5% significance level and power of 80%, 36 participants (accounting for 20% attrition rate) was sufficient to demonstrate a 25% difference in proportions of excellent intubating conditions between patients undergoing general anaesthesia with rocuronium as the muscle relaxant followed by a flush versus without a flush.

Recruitment of study participants was done after eligibility assessment. Informed consent was obtained. This assessment and consenting were done during pre-anaesthesia review in the anaesthesia clinic or reviews in the ward. Random sampling was used during the day, between eight a.m. and five p.m. as the hospital only does elective cases during daytime hours (eight a.m. to five p.m.). The principal investigator had to be present for the patient explanation and during data collection.

All potential participants were taken through an explanation on the purpose and procedure of the study. Following this, written consent was sought.

This was a single-blind study; patients were blinded by being under general anaesthesia at the time of muscle relaxant administration and did not know their group allocation before induction. There were two anaesthesiologists involved, one administering the drugs, in this case, the principal investigator (not blinded) and the other performing the intubation and assessing intubating conditions (blinded). The anaesthesiologist/ senior anaesthesia trainee doing the intubation recorded the outcome of interest (intubating conditions) on the data collection tool immediately after the intubation. They were blinded using a drape at the time of drug administration. The one who was administering the drugs (principal investigator) was not blinded hence the single blinding.

The participants were randomly allocated to one of the two

arms, F (flush with rocuronium) or NF (rocuronium only) using simple randomization. A random allocation sequence was generated by a computer algorithm. The clinician screening the patient attached the envelope to the anaesthesia documentation (which stayed in the patients' medical records). Once the participant arrived in the pre-operative receiving area of the main theatres, the principal investigator received the envelope containing the allocation number (If misplaced, the envelope attached to the data collection tool/ consent form were used). The allocation number directed the arm in which the participant belonged to. The syringes were arranged as shown in figure 2 below before the study drug administration [22]. The three-way taps close to the patient were removed after intubation and the perfusion tubing connected directly to the patient's cannula.

Adult patients scheduled for elective surgery and were randomized to either receive 20 mls of saline following intravenous 0.6mg/kg Rocuronium or no saline following intravenous 0.6mg/kg Rocuronium. In both arms, participants had a running drip using a giving set inbuilt with a drip counter (diaflow) dialed to 250mls/hour for the time data was being collected. This would ensure a standard flow rate of the drip despite the varied cannula sizes (gauge 18 and 20). Participants were intubated at exactly one minute following the Rocuronium dose. Two anaesthesiologists were involved, one performing the intubation and the other administering the drugs (in this case the principal investigator). The anaesthetists performing the intubation were competent in intubation. This was defined as a resident who has completed at least two years of training [23]. Those included as intubating doctors were third and fourth-year residents, instructors and consultants. In our setting this would have corresponded to over 150 intubations previously done by the intubating doctor.

On arrival to the operating theatre, a blood pressure cuff, three lead electrocardiography, a pulse oximeter, and a thermometer were attached to obtain the baseline cardiovascular parameters.

Intravenous access was obtained using a gauge 18 or 20 cannula. The STIMPOD NMS 450X- monitor was calibrated before use to avoid erroneous readings [24]. The twitch monitor's distal electrode (cathode) was placed on the skin of the flexor crease of the ulnar aspect of the wrist where it is most superficial. The proximal electrode (anode) was placed two centimetres proximal to the cathode, parallel to tendon of flexor carpi ulnaris. This was on the contralateral hand to the intravenous access.

Supramaximal stimulation was achieved by placing the cathode at the point where the ulnar nerve is most superficial. A single impulse at two Hz with a single pulse wave of 0.2 milliseconds in duration for 1.5 seconds (s) at 30 mA was applied and repeated at one minute after muscle relaxant administrations. The Adductor pollicis muscle had an accelerometer attached to measure the contractions.

Patients positioning for the intubation was left at the discretion of the primary anaesthetist as the outcomes being measured were Jaw relaxation, vocal cord positioning, and

response to intubation. These parameters, especially vocal cord position could be assessed only if the anaesthetist had the patient in their most preferred position. All patients received 0.03mg/kg midazolam for anterograde amnesia as these patients were having total intravenous anaesthesia, which is known to have a higher risk of awareness [25]. 4ng/ml remifentanyl (Plasma targeted Minto model) [26] and 4mcg/ml of propofol (effector targeted Schneider model) [27] was administered via target-controlled infusion (pump model: injectomat TIVA agilio). Rocuronium was administered at the time both pumps achieve the effector site and plasma concentrations set and the timer started. Intubating doctor was shielded from the drugs being administered using a drape. Oral endotracheal intubation was done at one minute following rocuronium administration.

Hemodynamic and other monitoring parameters were recorded at the end of intubation to assess the change during intubation and as per standard practice during the rest of the anaesthesia.

In the event of an adverse event, in this case, an unanticipated difficult intubation, patients were to be subjected to the standard difficult airway algorithm. Additionally, a clinical incidence form was to be filled. Patients were to be informed of the adverse event to raise it in future anaesthetic encounters. Clear documentation in the patients' files was to be done. The rest of the care offered to the patient was at the discretion of the anaesthesiologist handling the case.

Neuromuscular block monitoring was started by the anaesthetic assistant immediately after the induction of anaesthesia. Use of accelerometry (STIMPOD NMS 450X)) at adductor pollicis of the arm contralateral to IV cannula was done per the guidelines for good clinical research practice in pharmacodynamic studies [28]. Patient details and baseline characteristics were recorded. Data collection tools indicating intubating conditions (the Goldberg scale) were filled by the intubating doctor.

### 3. Ethical Considerations

This study started after clearance from the institutional ethics review committee of the Aga Khan University. Written consent was obtained from the participants after explanation of the study was done.

### 4. Results

There were 62 participants assessed for eligibility, five did not meet inclusion criteria as two had liver disease and three declined to participate. Fifty-seven participants were included in the study, 29 in the saline flush group and 28 in the group without a saline flush. Two patients in the saline flush group were excluded due to a dysfunctional laryngoscope light at time of intubation and the other due to a disconnection of the nerve stimulator at one minute after rocuronium administration. Three patients had their surgery postponed or cancelled and two had their surgery converted

to emergency. Eventually 25 patients in each group were analysed. The flow diagram of patients during the study period is shown in figure 1. No adverse outcomes were noted with regards to drug reactions to rocuronium or adverse hemodynamic changes during the time of data collection.

Patients in both groups were comparable with respect to demographic profile i.e. age and sex ( $P > 0.05$ ). However, there was a statistically significant difference in the body mass index between the groups as shown by student t test ( $P=0.025$ ) (Table 2). There was no statically significant difference in the mean heart rate before and after intubation between the groups. However, there was a significant rise in mean heart rate after intubation in both groups ( $83.81 \pm 15.27$  beats per min vs.  $88.12 \pm 14.08$  beats per min,  $P < 0.05$ ). This suggests that the intubation process was associated with an increase in heart rate. This is however not clinically significant as it is below the 20% change from the baseline heart rate.

In the group with a flush, 18 (62.1%) patients had "excellent" and seven (33.3%) patients had "good" intubating conditions as opposed to 11 (37.9%) having "excellent" and 14 (66.7%) having "good" intubating condition in the group without a flush. The distribution of intubating conditions for the two groups showed a difference of 24.2% in the proportion of patients with excellent intubating conditions which was statistically significant ( $P=0.042$ ). No patients had "poor" intubating conditions in the two groups (table 3). The worst scoring participant had a score of six out of the possible 12 points.

The twitch height was depressed more in the saline flush group (mean 38.00, S.D 17.09) compared to the no saline flush group (mean 27.88, S.D 11.62). This was found to be statistically significant ( $P. 0.031$ ) as shown in table 5. There was no relationship between intubating conditions and the twitch height depression from baseline at the one minute mark between the two groups ( $P=0.682$ ) as shown in table 6.

### 5. Discussion

In this study, it was found that a 20 ml saline flush immediately after rocuronium 0.6mg/kg had 62.1% of patients having excellent intubating conditions and 100% with acceptable (excellent and good) intubating conditions. Gore et al achieved 66% with acceptable intubating conditions with propofol 2.5 milligrams per kilogram without muscle relaxants [29]. McCourt et al found 65% excellent conditions and 97% acceptable conditions with rocuronium after 60 seconds of fentanyl and thiopentone anaesthesia [30]. Weiss et al found 40% acceptable intubating conditions following rocuronium 0.7mg/kg which is lower than our study findings [4]. Larsen PB et al in 2005 found 96% acceptable intubating conditions with rocuronium comparable to our findings [31].

The 20 ml saline flush increased the proportion of patients with excellent intubating conditions from 37.9% to 62.1% in this study. This corresponds to an increase of 24.2% increase. This comparison of rocuronium with and without a flush has

not been studied before. The comparisons between proportions of excellent intubating conditions of suxamethonium and rocuronium have shown 25% in McCourt et al and 36% in Menke et al study [30, 21].

This observed change in proportion of patients with excellent intubating conditions shows that the saline flush could have aided the onset of rocuronium (0.6 mg/kg) as opposed to 0.6mg/kg rocuronium dose with no saline flush. This quicker onset in the saline flush group as shown in table 5 could be one of the reasons we had better intubating conditions in this group.

The onset time of rocuronium was assessed at the one minute mark by the degree of twitch height depression. A greater average depression of the twitch height seen in the group with a 20 ml saline flush is points towards a quicker onset time in that group (table 5). Ishigaki et al showed that a saline flush shortens the onset of action time of muscle relaxants as assessed by the train of four monitoring [22]. This could be the reason for the better intubation conditions as rocuronium is delivered to the central circulation and hence to the muscles faster with the aid of a flush. Nevertheless, as shown in table 6, twitch height depression at the one minute mark on its own could not predict the intubating conditions of a patient.

This study had several limitations first, we did not assess the time taken to intubate these patients as this would be a good marker of failed intubations. It was seen that there were no patients with “poor” intubating conditions in both groups (Goldberg score between seven and twelve). The additional effects of the opioid analgesic in obtunding the response to laryngoscopy and propofol depression of upper airway reflexes could be additional factors explaining the above. More so exclusion of patients suspected to have a difficult airway may have explained this. We did not standardize the intubating techniques as the use of adjuvants such as pillows, patient positioning, and type of laryngoscope was left at the discretion of the primary anaesthetist to ensure no change in usual practice other than the intervention used in the study. Double blinding rather than single blinding could have made the study more robust as well. In this study, the participants had no impact on the outcome as they were anesthetized. Nevertheless, the principal investigator was not blinded even though they didn’t assess the primary outcome of interest (in this case intubating condition). The assessing doctor was blinded as to which arm the patient belonged to and thus

couldn’t bias their assessment of intubation. There was no formal training on the assessment of intubating conditions given to the intubating doctors.

The assessment tool was informally explained to the intubating doctor before starting the anaesthetic. In retrospect, formal training would have improved the reliability of the intubating doctors’ assessment. Other factors especially patient factors that would have affected the onset of action time of rocuronium could have affected the results of this study, there include but not limited to hypo-/hyperkalaemia, hypo-/hypomagnesemia, hypo-/hypercalcemia, respiratory acidosis/alkalosis, liver dysfunction and Eaton- Lambert syndrome. In our study, we were limited in resources to standardize all these factors and our patients do not routinely get all these tests preoperatively making this a limitation of the study. Ideally, the remifentanyl and the propofol should have been administered through a different IV line.

The other limitation is that the study was done in elective patients with stable hemodynamic parameters and more studies need to be done to assess this effect in patients in emergencies with unstable hemodynamics requiring rapid sequence intubation. The study was also a single-centre study and hence expertise in intubation was limited to the institutional standards. The sample size was also small. The finding that there was a statistically significant difference in body mass index between the two groups, more on the saline flush group could mean that they received a higher dose of rocuronium and hence making it difficult to attribute the results solely to the effect of the 20 ml saline flush (table 2). However, both groups had a BMI within the overweight category hence making it difficult to derive clinical significance. Additional and potential limitations may still exist.

## 6. Conclusion

In this group of patients studied, the administration of a 20 ml saline flush after 0.6mg/kg rocuronium increases the proportion of patients with excellent intubating conditions as compared to rocuronium without a saline flush. This allows better intubating conditions intubation at one minute with a lower dose of rocuronium (0.6mg/kg) as opposed to higher doses (0.9-1.2 mg/ kg) which may be associated with prolonged duration of action which may be undesirable in various conditions.

## Appendix

*Table 1. Goldberg Scale of intubation conditions.*

Score	Ease of intubation	Vocal cords	Response to intubation
1	Good	Open full	None
2	Fair	Open midday	Diaphragmatic movement
3	Difficult	Movement	Moderate coughing
4	Poor	Closed	Severe coughing or bucking

\* Total score of 3 for excellent intubation conditions, 4–6 good, 7–9 poor, 10–12 inadequate or failed. Reproduced from: Goldberg ME, Larijani, Azad SS, et al. Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. *Anesth Analg*. 1989; 69: 93–9.

**Table 2.** Demographic variables between the two groups as shown by the independent sample student t-test for age and Body mass index and Pearson's Chi-square test for gender.

Demographic variable	Total N=52	Without flush N=27	With flush N=25	p-value
Age (SD)	38.65 (SD12.40)	39.48 (SD12.61)	37.89 (SD12.37)	0.648
Gender				
Male	22 (42.31%)	10 (40%)	12 (44.4%)	0.785
Female	30 (57.70%)	15 (60%)	15 (55.6%)	
BMI in Kg/M <sup>2</sup> (SD)	26.09 (SD3.36)	25.03 (SD2,65)	27.17 (SD3.72)	0.025

**Table 3.** Comparison of the proportion of patients in the different categories of intubating conditions between the groups by Chi-Square test.

	Without flush N=25	With flush N=25	p-value
Excellent	N=11 (37.9%)	N=18 (62.1%)	0.042
Good	N=14 (67.7%)	N=7 (33.3%)	

**Table 4.** Intubating conditions absolute values between the groups.

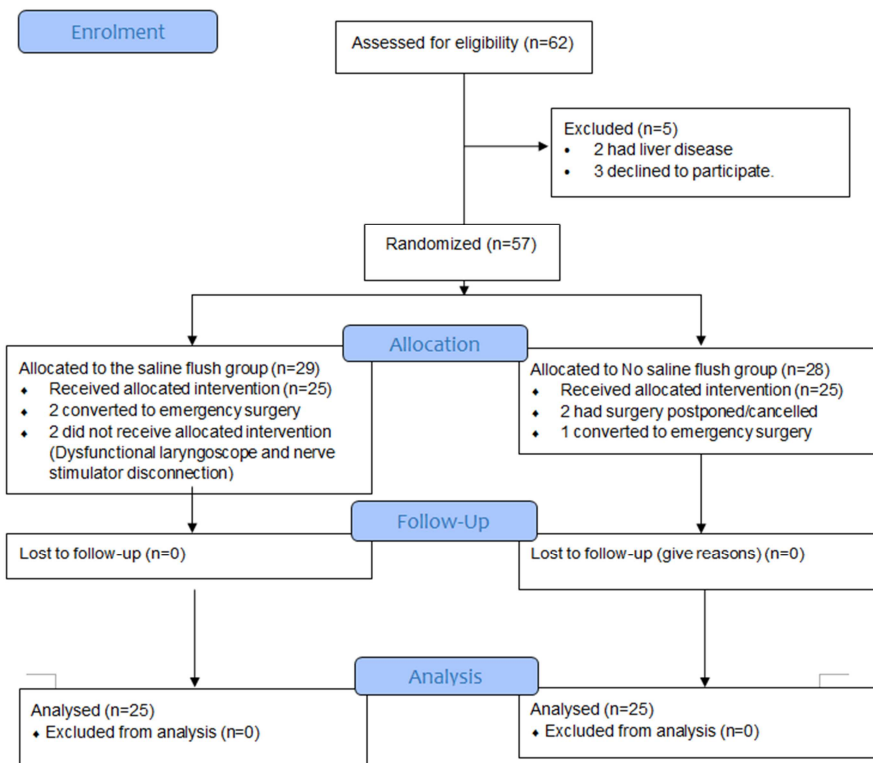
	3	4	5	6	7-12
Without flush	11 (44.0%)	11 (44.0%)	1 (4.0%)	2 (8.0%)	0 (0%)
With flush	18 (72.0%)	5 (20.0%)	1 (4.0%)	1 (4.0%)	0 (0%)

**Table 5.** Average change in twitch height (where change in twitch height is the difference between baseline twitch height and twitch height at one minute following muscle relaxant administration) between the groups shown by independent sample student t-test.

Total	Without flush N=25	With flush N=25	p-value
Average change in Twitch height from baseline	27.88 (S.D 11.62)	38.00 (S.D 17.09)	0.031

**Table 6.** Comparison between intubating conditions against the average twitch height depression as shown by independent sample student t-test.

Total	Good N=21	Excellent N=29	p-value
Average change in twitch height	34.14 (S.D 15.23)	32.07 (S.D 15.62)	0.682



**Figure 1.** CONSORT Flow Diagram.

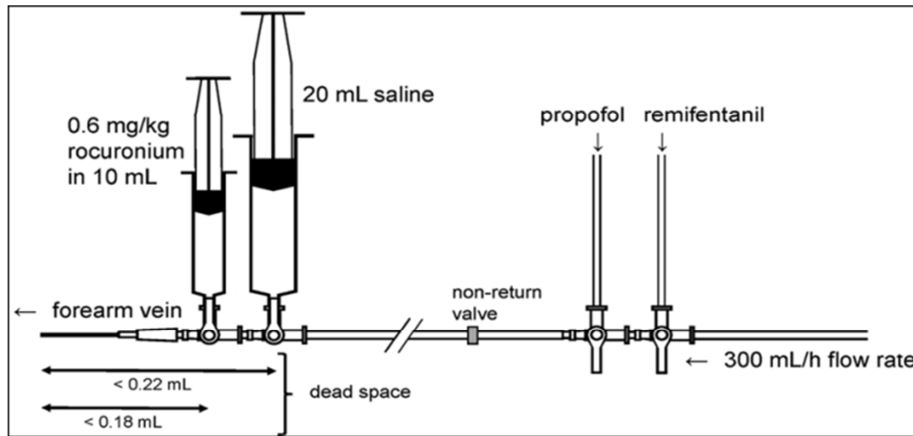


Figure 2. Arrangement of perfusion tubing.

From Ishigaki S, Masui K, Kazama T. Saline Flush After Rocuronium Bolus Reduces Onset Time and Prolongs Duration of Effect: A Randomized Clinical Trial. *Anesth Analg.* 2016; 122 (3): 706-711. <https://doi.org/10.1213/ANE.0000000000001094>

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