Efficacy and safety of remifentanil in a rapid sequence induction in elderly patients: A three-arm parallel, double blind, randomised controlled trial

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Efficacy and Safety of Remifentanil in a Rapid Sequence Induction in elderly patients: a three-arm parallel double blind randomised controlled trial.

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ABSTRACT

Background:

Rapid sequence induction (RSI) is recommended in patients at risk of aspiration, but induced hemodynamic adverse events, including tachycardia. In elderly patients, this trial aimed to assess the impact of the addition of remifentanil during RSI on the occurrence of: tachycardia (primary outcome), hypertension (due to intubation) nor hypotension (remifentanil).

Methods:

In this three-arm parallel, double blind, multicentre controlled study, elderly patients (65 to 90 years old) hospitalised in three centres and requiring RSI were randomly allocated to three groups, where anaesthesia was induced with etomidate (0.3 mg/kg) followed within 15 seconds by either placebo, or low (0.5 µg/kg), or high (1.0 µg/kg) doses of Remifentanil, followed by succinylcholine 1.0 mg/kg. Heart rate (HR) and mean arterial pressure (MAP) were recorded before induction and after intubation.

Results:

In total, eighty patients were randomised and analysed. Baseline HR and MAP were similar between groups. For primary endpoint, the absolute change in HR between induction and intubation was greater in the control group (15 bpm; 95% CI [8-21]) than that in the remifentanil 0.5 µg/kg group (4 bpm; 95% CI [-1-+8]; $p = 0.005$) and the remifentanil 1.0 µg/kg group (-3 bpm; 95% CI [-9-+3]; $p < 0.0001$). The increase in MAP was greater in the placebo group than in both remifentanil groups ($p < 0.0001$). Twice as many hypertension episodes were recorded in the placebo group compared to the remifentanil 0.5 µg/kg and 1.0 µg/kg groups (60%, 30%, and 28% patients respectively; $p = 0.032$), but no placebo patients experienced hypotension episodes *versus* 11% and 24% in the remifentanil 0.5 µg/kg and 1.0 µg/kg groups respectively ($p = 0.016$).

Conclusion:

Remifentanil (0.5-1.0 µg/kg) prevents the occurrence of tachycardia and hypertension in elderly patients requiring RSI.

INTRODUCTION

Rapid sequence induction (RSI) and Sellick manoeuvre are recommended in patients at risk of regurgitation and aspiration to prevent pulmonary morbidity (1-4). In order to quickly protect the airway, drugs with rapid onset such as etomidate, propofol, ketamine or thiopenthal are routinely used in combination with succinylcholine (5). In elderly patients, etomidate is preferred, as it provides a greater haemodynamic stability compared to propofol or thiopental and more rapid emergence, while ketamine induced more postoperative *delirium* (6-8). However, the occurrence of tachycardia and hypertension leading to deleterious cardiac sides effects is often reported (9-12). To prevent these potential complications, opioids are commonly used in clinical practice (13). Indeed, in 2016, a national survey conducted in the United Kingdom reported that 75% of anaesthetists use opioids for RSI (14). However, currently, there is no recommendation concerning the use of opioids in RSI, as they could cause regurgitation and potentially aspiration (15).

Remifentanil is a synthetic opioid with rapid onset and short duration (16-18). Its short-acting pharmacokinetic profile allows the co-administration of remifentanil with the hypnotic: after an intravenous bolus the plasma concentration immediately rises. O'Hare et al. reported that the co-administration of thiopental with remifentanil 1 µg/kg provides haemodynamic stability with neither tachycardia nor hypotension in a population of healthy patients under 65 years old (19). In contrast, a greater dose (1.25 µg/kg) was associated with more episodes of hypotension. In 2013, Alanoglu et al. tested remifentanil bolus (0.5 µg/kg and 1.0 µg/kg) during RSI, without significant haemodynamic changes *versus* placebo, but they used propofol in a population aged less than 65 years (20).

Co-administration of etomidate and remifentanil could be of particular interest in elderly patients. Indeed, these drugs could be effective to prevent tachycardia and hypertension

during RSI without inducing deleterious hypotension in this population. Therefore, the primary objective of this study was to assess the impact of co-administration of remifentanil at two different doses (0.5 µg/kg and 1 µg/kg) on the occurrence of tachycardia during RSI in elderly patients. Secondary objectives were to assess the occurrence of hypotension and hypertension and evaluate intubation conditions between the groups. We hypothesised that the administration of remifentanil would prevent tachycardia during RSI.

METHODS:

The present multicentre (Nîmes University Hospital, Nîmes, France; Polyclinique Grand Sud Institute, Nîmes, France and Canadian University Hospital Maisonneuve-Rosemont, Canada), three-arm parallel, randomised, double blind, superiority, controlled trial was approved by the local ethics committee of Nîmes, France (Comité de Protection des Personnes, 2010.04.03, EudraCT n°2009-018169-12) and by local ethics committee of Hospital Maisonneuve-Rosemont, Canada (IRB, 04/2010). All patients gave their written informed consent. The study was registered at ClinicalTrials.gov (NCT01259648), and conducted in accordance to the original protocol. The full trial protocol can be accessed by request to the corresponding author.

Participants

We included patients between 65 to 90 years old, requiring RSI during pre-anaesthesia consultation. This procedure was indicated in patients requiring invasive mechanical ventilation with a risk of aspiration (full stomach contents, obese or diabetes mellitus patients with gastroparesis, and severe gastroesophageal reflux).

Patients were not included when the anaesthetic agents being studied were contraindicated, when body mass index (BMI) was > 40 kg/m^2, and when a patient's haemodynamic status was assessed as unstable by the physician in charge.

Interventions and anaesthetic management

Patients were not premedicated. After three-minute preoxygenation, anaesthesia was induced with etomidate 0.3 mg/kg administered in five seconds, followed within 15 seconds by either placebo (20 ml normal saline, control group) or low dose of remifentanil (remifentanil 0.5 µg/kg group) or high dose of remifentanil (remifentanil 1.0µg/kg group), by bolus infusion in 20 seconds. Succinylcholine 1.0 mg/kg was administered in five seconds after administration of the study drug. Once the patient was unconscious, cricoid pressure (Sellick manoeuvre)

was performed. Neuromuscular block was monitored with acceleromyography using train-of-four (TOF) stimuli and tracheal intubation was performed via laryngoscopy when TOF indicated the absence of any responses (0/4). If tracheal intubation was difficult, standard French guidelines for management of the difficult airway were followed. When the trachea was intubated, mechanical ventilation was applied to obtain SpO_2 > 95% and $EtCO_2$ between 30-40 mmHg. Anaesthesia was maintained by inspired Sevoflurane 1% without stimulations for five minutes. Blood arterial pressure and HR were non-invasively monitored following our routine anaesthetic practice.

During this procedure, fluid administration was performed using normal saline (5 ml/kg/h).

When systolic arterial pressure was ≤ 80mmHg, 50 µg phenylephrine or 10 mg ephedrine could be given according to the concomitant presence of bradycardia (HR < 45 bpm). When systolic arterial pressure was ≥ 180 mmHg, 0.3 mg/kg propofol could be given. When HR was < 45 bpm, 1 mg atropine or 10 mg ephedrine could be given according to the concomitant presence of low systolic blood pressure (≤ 80 mmHg).

Randomisation and blinding

Patients were randomly assigned in a 1:1:1 ratio to the study drugs (20 ml normal saline, remifentanil 0.5 µg/kg or 1.0 µg/kg made up to 20 ml with normal saline) according to a randomisation list stratified on the centre and with fixed blocks. This list was established using computer-generated random numbers (SAS software) by the methodologist of the Biostatistics Department of Nîmes University Hospital appointed to the study. Random sequence allocation was centralised to an online application to which recruiting investigators had access via connection with personal login and password. Randomisation was independent of recruiting investigators and patients, who were blinded to treatment assignment. The only person aware of the treatment administered was the independent nurse who opened the envelope containing the randomisation assignment and

prepared the syringe containing the study drug or placebo, but did not participate in the RSI or anaesthetic management. The placebo and remifentanil medications had an identical appearance. The statistician was kept blinded to the treatment assigned until all statistical analyses were performed.

Outcomes

Heart rate (HR) and mean arterial pressure (MAP) were recorded at baseline (inclusion visit), before and after preoxygenation (t0 and t1), after induction (t2), immediately after intubation (t3) and every minute for five minutes after intubation (t4 to t8).

Patient age, sex, weight, height, surgical procedure, results of airway assessments (Mallampati status, thyromental distance, mouth opening, and neck mobility), ASA status, use of beta blocker medication at home and the RSI indication were recorded.

The primary outcome was to determine whether the administration of remifentanil (0.5 or 1.0 µg/kg) could reduce intubation-dependent tachycardia (absolute change in HR between t0 and t3). For this purpose, a 13-bpm reduction in HR was expected in patients given remifentanil 0.5 or 1.0 µg/kg compared to the control group, according to the literature (19).

The secondary outcomes were: (i) MAP absolute variation following RSI; (ii) occurrence of high blood pressure episodes (Systolic arterial pressure > 180 mmHg) requiring propofol infusion; (iii) occurrence of hypotension (SAP < 90 mmHg) requiring vasopressors; and (iv) evaluation of intubation conditions, and Cormack scale. The ease of laryngoscopy, jaw relaxation, resistance to blade, position and movement of vocal cords, movement of the limbs and coughing were recorded and graded as excellent, good or poor.

Sample size calculation and statistical analysis

With an alpha risk = 0.05 and a beta risk = 0.8, twenty-five patients per group were needed for the anticipated reduction in HR of 13 bpm (19).

Statistical analyses were performed using SAS© (SAS Institute, Cary, NC, USA) version 9.4 and R 3.0.2 (R Development Core Team (2014), R Foundation for Statistical Computing, Vienna, Austria) using a 2-sided type 1 error rate of 0.05 as the threshold for global test statistical significance and 0.025 as the threshold for the two comparisons (Bonferroni correction). Quantitative data are expressed as mean ± standard deviation. Qualitative variables are expressed as frequency with percentage. The quantitative criteria (absolute change in HR and in MAP) were compared between the three groups by an ANOVA. The qualitative criteria (occurrence of hypertension or hypotension episodes, need for supplementary medication, and intubation conditions) were compared between the three groups by a chi-square test or a Fisher exact test. A linear mixed model was constructed for HR and MAP over time to estimate the treatment effect (fixed effect) by taking into account the nine time points of the follow-up by patient (random slope and random intercept), and adjusting on the potential confounding factors (fixed effects), particularly the centre. Occurrences of HR or MAP peak (tachycardia, hypotension or hypertension) were assessed with quadratic and cubic time effects.

RESULTS:

Patients

From March 2011 to May 2014, eighty-two patients were included into the study. One patient did not receive RSI for his anaesthesia and one patient was included twice during the inclusion period. Therefore, statistical analysis was performed on 80 patients. Patient flow is shown in Figure 1.

Baseline patient characteristics are summarised in Table 1. Of note, a higher proportion of women were assigned to group remifentanil 0.5 µg/kg as compared to the other groups (67%, 50% and 42% for remifentanil 0.5 µg/kg group, placebo and remifentanil 1.0 µg/kg group respectively). Blood pressure (systolic, diastolic, mean) and HR were similar in all three groups.

During RSI, no patients experienced desaturation nor requested mask ventilation. Furthermore, no patients coughed or moved during the procedure.

Primary outcome

Between t0 (preoxygenation) and t3 (intubation), the absolute change in HR was greater in the control group (15 bpm; 95% CI [8-21]) than that in the remifentanil 0.5 µg/kg (4 bpm; 95% CI [-1-+8]; $p = 0.005$) and remifentanil 1.0 µg/kg groups (-3 bpm; 95% CI [-9-+3]; $p < 0.0001$) (Table 2).

The HR across the time points is shown in Figure 2A. A statistical difference was observed between control group and remifentanil groups at t4 and t5 (Figure 2). The linear mixed model for HR over time (t0-t9) showed a statistical difference between remifentanil 1 µg/kg and placebo ($p = 0.02$) with no sex or centre difference.

Secondary outcomes

MAP over time is shown in Figure 2B. The increase in MAP was lower in the remifentanil groups in a dose-dependent manner ($p < 0.0001$) (Table 2, Figure 2). The number of

hypertension episodes requiring propofol injection was greater in the placebo group than in the remifentanil 0.5 µg/k and remifentanil 1.0 µg/kg groups (60 % (IC 95 [38.80; 77.61]), 30 % (IC 95% [13.75; 50.18]) and 28% (IC 95% [12.07; 49.39]) respectively; $p = 0.032$). Patients with severe hypotension after induction were 0 in placebo group *versus* 5 in remifentanil 0.5 µg/kg and 6 in remifentanil 1 µg/kg. The numbers of patients requiring one bolus of ephedrine after induction was: 0 in placebo group, 3 in remifentanil 0.5 µg/kg (*versus* placebo, $p = 0.23$), and 6 in remifentanil 1 µg/kg (*versus* placebo, $p = 0.0087$). No difference was observed between remifentanil groups ($p = 0.28$). The linear mixed model for MAP over time (t0-t9) showed a statistical difference between remifentanil 1 µg/kg and placebo ($p = 0.001$) with no sex difference. There was no difference in intubation conditions evaluation between the three groups ($p = 0.424$) (Table 2).

Complementary analyses

The changes in HR and MAP for the entire follow-up (nine time points) are shown in Figure 2. By adjusting on the recruiting centre and the sex in the two linear mixed models ($n = 80$ for each model), the same trends as in the crude analyses were found: lower HR, lower tachycardia peak, lower MAP and lower hypertension peak with remifentanil with the dose response effect (data not shown).

DISCUSSION

In this prospective, multicentre, double blind, randomised controlled trial involving 82 elderly patients requiring a RSI with etomidate and succinylcholine, the administration of low (0.5 µg/kg) and high (1 µg/kg) dose of remifentanil decreased tachycardia during tracheal intubation. Cases of hypotension requiring vasopressor drugs occurred in a dose-dependent manner. These findings suggest that at induction of anaesthesia, 0.5 µg/kg remifentanil provides a more stable haemodynamic condition than placebo and 1 µg/kg remifentanil in elderly patients.

RSI is indicated when a risk of aspiration exists (2). In these conditions, anaesthetic induction aims to decrease the time for tracheal intubation and avoid drugs that could induce aspiration and vomiting. To reduce the time to tracheal intubation, drugs with rapid onset are routinely used, and for elderly patients etomidate is indicated because it provides stable haemodynamic conditions (21). Although opioids are not recommended for preventing regurgitation during tracheal intubation, performing the procedure without opioids could lead to tachycardia and hypertension that could be deleterious in elderly patients. Edwards et al. reported that a greater use of rate-pressure products during tracheal intubation and extubation in patients undergoing different surgical procedures was significantly associated with myocardial ischemia using electrocardiogram monitoring (10). Similarly, Stone et al. reported that myocardial ischemia was more frequent in hypertensive patients when tachycardia and nociceptive stimulation occurred (9). Moreover, hypotension has been shown to be associated with poor outcome. Mangano et al. reported the deleterious effect of hypotension and tachycardia on myocardial oxygen balance in cardiac and non-cardiac surgery patients (22). Hirsch et al. recently reported an association between hypotension and episodes of confusion after non-cardiac surgery (23).

This study clearly shows that remifentanil prevents the occurrence of tachycardia and hypertension at both 0.5 and 1 µg/kg doses. Moreover, a dose of 0.5 µg/kg remifentanil causes fewer episodes of hypotension requiring vasopressor drugs as compared to the higher dose tested (1 µg/kg). As hypotension episodes have been shown to be associated with poor patient outcome, we can assume that the use of low dose remifentanil is advisable for providing stable haemodynamic condition during tracheal intubation in elderly patients. In this study, the recording of ST segment and intra or postoperative troponin were not performed but could have emphasised the results of the present study, as reported previously (9, 10, 22, 23).

The role of Beta-adrenergic blocking agent in the prevention of perioperative ischemia is controversial and has been able to minimise episodes of tachycardia in patients treated during intubation (24). In our study, the distribution of these patients is not significantly different between the groups and their low number does not allow making one under analysis. Nevertheless, this population is at risk of intraoperative haemodynamic complications with high doses of remifentanil and encourages caution.

To date, no official guideline for the management of RSI and its complications is available. Although opioids such as remifentanil are often used, no study has so far addressed the simple question of whether remifentanil is efficient in reducing intubation-dependent tachycardia in elderly patients. Therefore, our findings can guide clinicians' decision-making for the use of opioids during RSI in this population.

However, before extrapolating these findings as a recommendation for all elderly patients requiring RSI, some limitations should be noted: first, ischemia was not monitored using electrocardiogram management and postoperative troponin measures. Intraoperative fluid management and vasopressor used in the this study were at the discretion of the anaesthesiologist, so that troponin or ST segment measures would have be questioned by

varied intraoperative anaesthetic and surgical conditions. However, the haemodynamic stability observed during the present study could be expected to prevent such ischemia episodes (9, 10). Second, we did not explore all features of patient outcome such as delirium. Third, this study was underpowered for opioid safety over induction due to regurgitation or aspiration occurrences. A study with a larger number of patients is necessary to attest the safety of this practice, as reported for the effect of cricoid pressure (compared with a sham for RSI) that included more than 34,000 patients (25). These limitations suggest that an ancillary study, assessing all these points, may help strengthen the interpretation of our findings. Moreover, the recording of at least the ST segment and postoperative troponin would have been useful as well as delirium and confusion.

In conclusion, remifentanil administered at 0.5 or 1.0 µg/kg prevents the occurrence of tachycardia and hypertension in elderly patients during RSI. However, it is advisable to use 0.5 µg/kg, as remifentanil 1.0 µg/kg induces more hypotension episodes than remifentanil 0.5 µg/kg.

Legend of the figures:

Figure 1: Flow chart

Figure 2A: Heart rate (HR) between groups at baseline (before preoxygenation, t0), after preoxygenation (t1), after induction (t2), immediately after intubation (t3) and every minute for five minutes after intubation (t3 to t8). Box-plot ("minimum", first quartile (Q1), median, third quartile (Q3), and "maximum").

Figure 2B: Mean Arterial blood Pressure (MAP) between groups at baseline (before preoxygenation, t0), after preoxygenation (t1), after induction (t2), immediately after intubation (t3) and every minute for five minutes after intubation (t3 to t8). Box-plot ("minimum", first quartile (Q1), median, third quartile (Q3), and "maximum").

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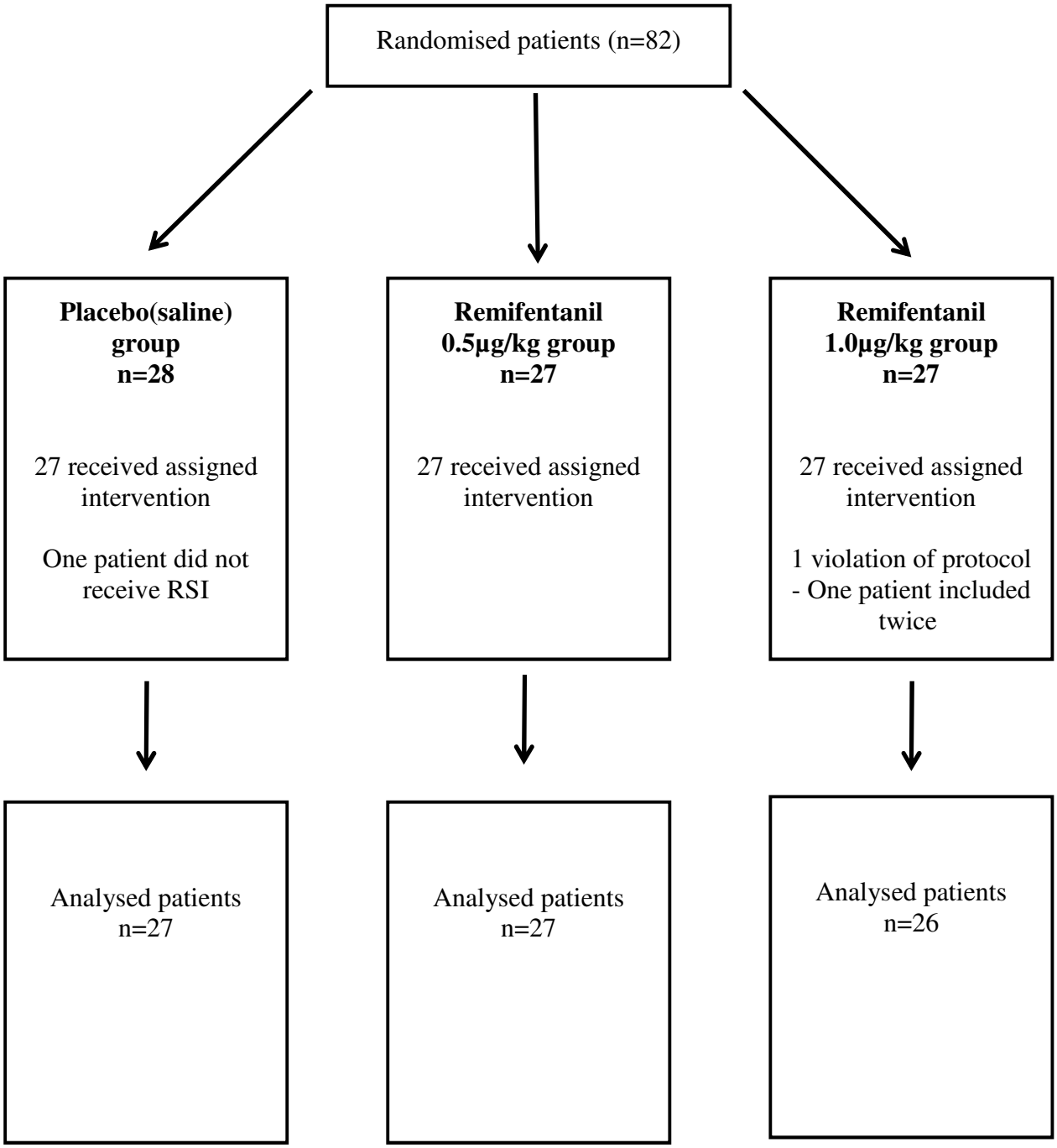
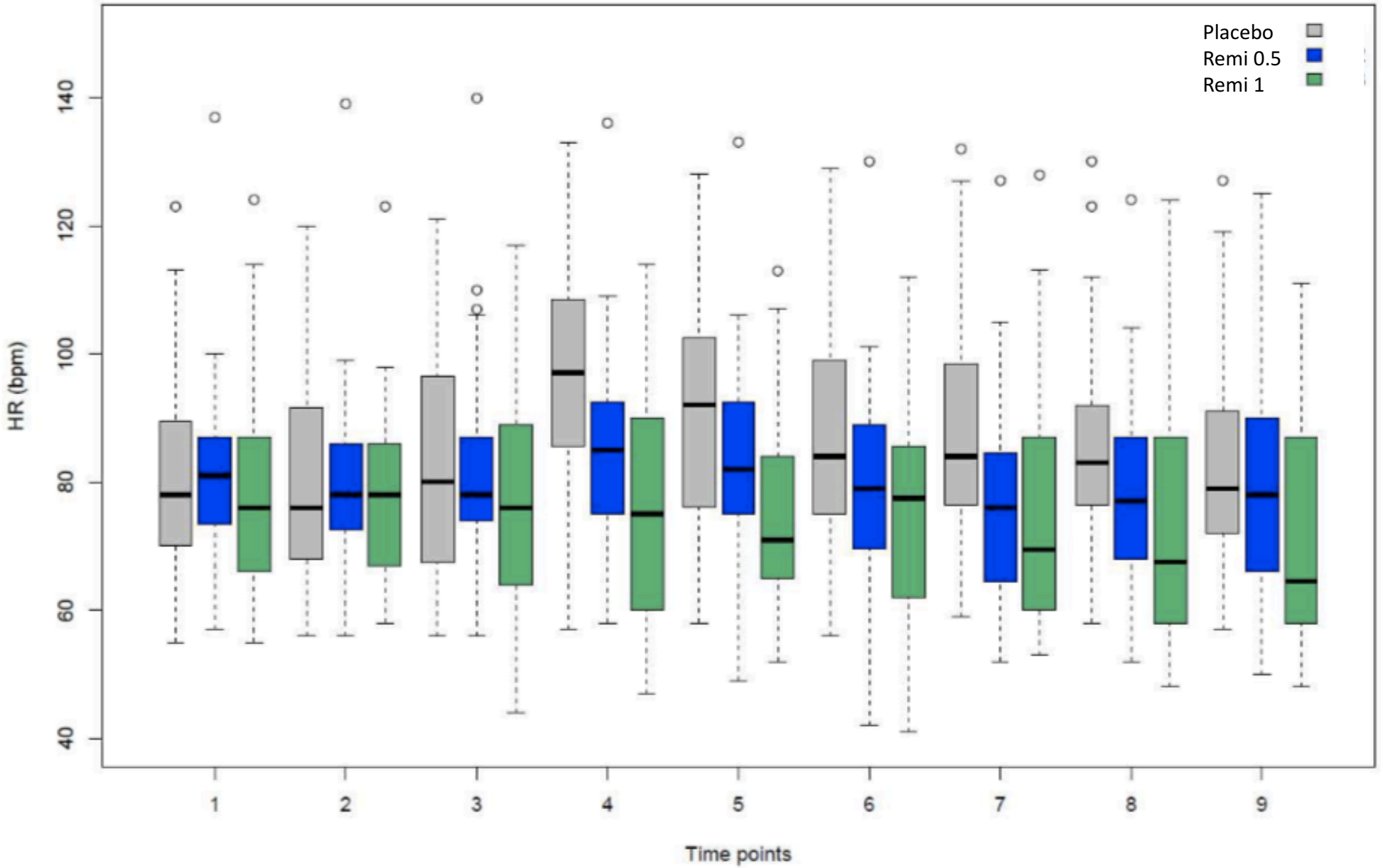
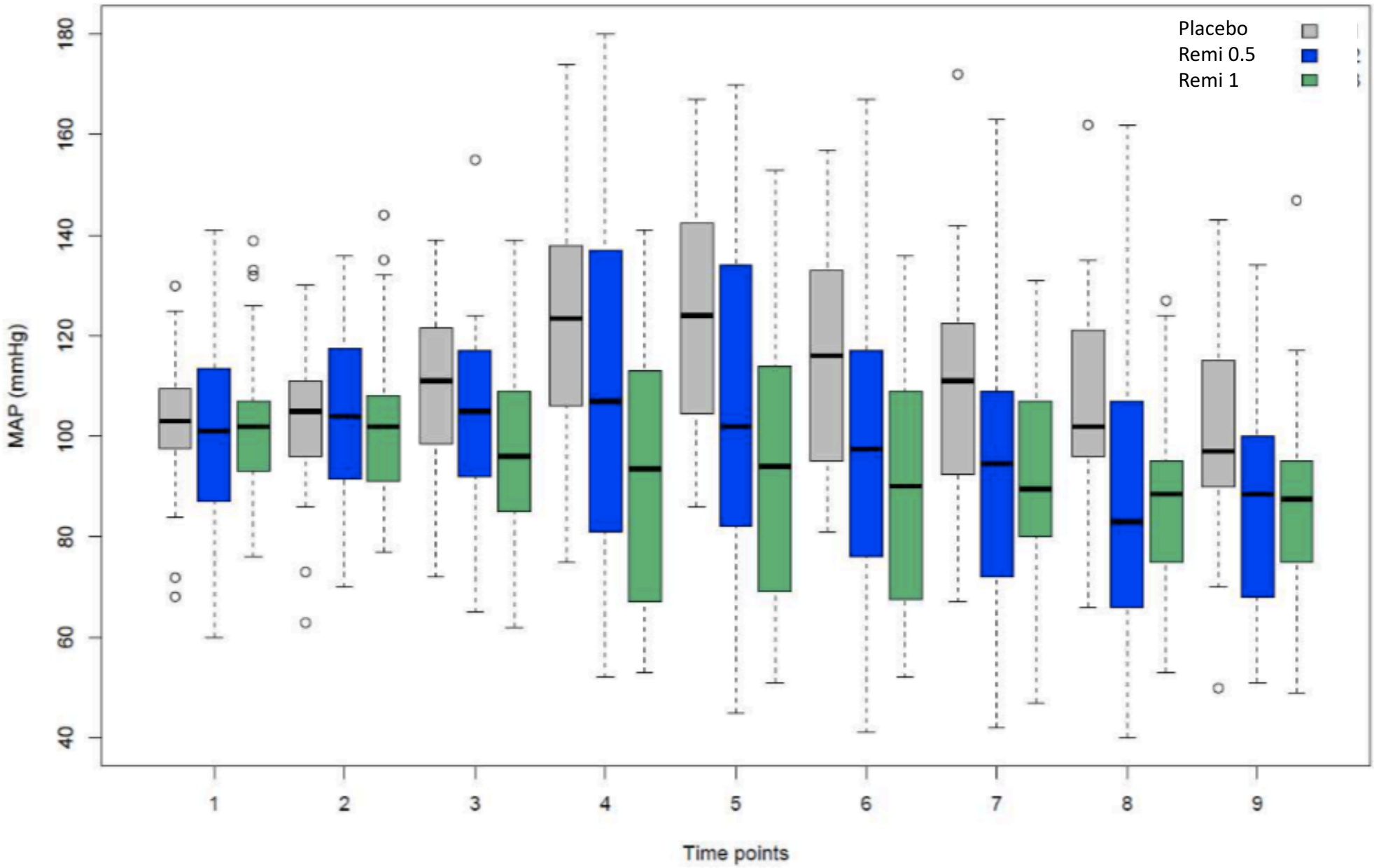
Figure 1: Flow chart




Placebo
Remi 0.5
Remi 1
HR (bpm)
40
60
80
100
120
140
1
2
3
4
5
6
7
8
9
Time points


Placebo
Remi 0.5
Remi 1
MAP (mmHg)
40
60
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180
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2
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6
7
8
9
Time points

Table 1: Patient characteristics (sex, age (yr), height (cm), weight (kg), systolic (SAP mmHg), diastolic (DAP mmHg) and mean (MAP mmHg) arterial pressures, heart rate (HR beat min-1) ASA)

	Placebo n=27	Remifentanil 0.5µg/kg group n=27	Remifentanil 1.0µg/kg group n=26
Age (years)	77 (± 7)	79 (± 6)	76 (± 6)
Female	14 (50%)	18 (67%)	11 (42%)
BMI	25 (± 4)	26 (± 4)	27-(± 5)
HR baseline *	79 (± 17)	83 (± 11)	82 (± 22)
SAP baseline *	149 (± 24)	143 (± 22)	144-(± 16)
DAP baseline *	78 (± 10)	75 (± 13)	78 (± 11)
MAP baseline *	102 (± 12)	98 (± 15)	100 (± 11)
HR t0†	81 (± 17)	82 (± 15)	79 (± 16)
SAP t0†	151 (± 24)	149 (± 32)	152 (± 23)
DAP t0†	78 (± 13)	78 (± 16)	79 (± 14)
MAP t0†	102 (± 154)	102 (± 20)	104 (± 15)
ASA 2†	13 (48%)	11 (41%)	14 (54%)
ASA 3†	13 (48%)	15 (55%)	11 (42%)
ASA 4†	1 (4%)	1 (4%)	1 (4%)
Emergency surgery†	20 (74%)	21 (78%)	13 (50%)
Indication†			
Full stomach contents	21 (78%)	25 (92%)	19 (73%)
Gastroesophageal reflux	4 (15%)	1 (4%)	7 (27%)
Gastroparesia	2 (7%)	1 (4%)	0 (0%)
Mallampati 1*	12 (44%)	15 (58%)	12 (46%)
Mallampati 2*	11 (41%)	8 (31%)	12 (46%)
Mallampati 3*	4 (15%)	3 (11%)	2 (8%)
Mouth opening > 35 mm**	25 (96%)	26 (100%)	25 (96%)
Thyromental distance >65 mm**	25 (96%)	25 (96%)	25 (96%)
Normal neck mobility**	25 (96%)	25 (96%)	24 (92%)
Preoperative medication: Beta-adrenergic blocking agent	7 (25%)	4 (15%)	5 (19%)

Results are presented as mean ± standard deviation or frequency with percentage. (n = number of analysed patients)

* One missing value in the Placebo group (the patient who did not receive RSI) and one missing value in the Remifentanil 1.0µg/kg group.

† One missing value in the Placebo group (the patient who did not receive RSI).

** Two missing value in the Placebo group (one patient who did not receive RSI) and one missing value in the Remifentanil 0.5 µg/kg group

Table 2: Courses of heart rate (HR), mean arterial pressures (MAP) and intubation conditions

	Placebo n=27	Remifentanil 0.5µg/kg group n=27	Remifentanil 1.0µg/kg group n=26	p-value
Primary outcome				
HR t0 (preoxygenation)	81 (±17)	82 (±154)	79 (± 6)	
HR t3 (intubation)	96 (± 17)	86 (± 17)	76 (± 17)	
Absolute change in HR	+15[+8; +21]	+ 4 [-1; +8]	- 3 [-9; +3]	< 0.0001
Secondary outcomes*				
MAP t0 (preoxygenation)	102 (± 15)	102 (± 20)	104 (± 15)	
MAP t3 (intubation)	123 (± 26)	108 (± 34)	92 (± 26)	
Absolute change in MAP	+21 [+11; +31]	+6 [-4 ; +16]	- 12 [-23; -1]	< 0.0001
Secondary outcome**				
Excellent intubation condition	20 (74%) [54%; 89%]	15 (58%) [37%; 77%]	18 (72%) [51%; 88%]	0.4244
Good intubation condition	7 (26%) [11%; 46%]	9 (34%) [17%; 56%]	7 (28%) [12%; 49%]	
Poor intubation condition	0	2 (8%) [1%; 25%]	0	

Results are presented as mean (± standard deviation) or [CI95%]. (n = number of analysed patients)

* One missing value in the Placebo group and one missing value in the Remifentanil 0.5µg/kg group.

** One missing value in the Remifentanil 0.5µg/kg group and one missing value in the Remifentanil 1.0µg/kg.