Author's response to reviews

Title: Intubating conditions and side effects of propofol, remifentanil and sevoflurane compared with propofol, remifentanil and rocuronium: a randomised, prospective, clinical trial

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Author's response to reviews: see over
1. Comments made by the Editor

Specifically in the discussion indicate the avoidance of neuromuscular blockade not only increases the risk of difficult tracheal intubation but also difficult mask ventilation.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

We revised the manuscript according to the recommendations of the reviewers. We added a paragraph about the risk of difficult tracheal intubation and the risk of difficult mask ventilation, when neuromuscular blocking drugs are avoided (please see Reviewer 1).

Changes in the manuscript are highlighted (bold type, blue).
2. Reviewer Comments:

Reviewer #1

This is a well done study, but its results, unfortunately, were predictable. There was no reason to expect, in my opinion, that the addition of sevoflurane to remifentanil, especially at 0.5 MAC only, would provide acceptable intubating conditions in a large number of patients.

Indeed, there were a few studies which dealt with this issue; they used, however, sevoflurane solely or combined with remifentanil, but without propofol. We wanted to show that remifentanil can be used with a lower dosage when combined with propofol and sevoflurane. We used sevoflurane with 1.0 MAC (approx. 2.0 Vol%), not 0.5 MAC (Please see Abstract, Introduction and Methods’ sections).

The studies have shown that a very high concentration of Sevo (ED95 8%) is required to intubate the trachea during the inhalational induction, and even then the intubating conditions are inferior to the ones achieved with the neuromuscular blockers.

To clarify, we added the following sentences:

Sevoflurane was also used solely for tracheal intubation; the ED95 for tracheal intubation was 8.07 % (end-tidal concentration) [Kimura et al 1994]. To determine the exact necessary concentration, patients’ tracheas were intubated after maintaining sevoflurane for 20 minutes [Kimura et al 1994]; this is not practical in the clinical setting. Intubating conditions after induction with sevoflurane 6 % and N2O 66 % in O2 were comparable with succinylcholine 1.5 mg·kg\(^{-1}\); excellent intubating conditions were significantly increased in the succinylcholine group [Iamaroon et al 2001]. Mean arterial pressure and heart rate were significantly decreased immediately before tracheal
intubation in the patients with sevoflurane; the authors proposed this inhalational technique for patients, when succinylcholine is contraindicated [Iamaroon et al 2001]. Adding of remifentanil 2.0 µg·kg⁻¹ to sevoflurane 8 Vol% resulted in acceptable intubating conditions in 29 patients out of 30 patients [Cagiran et al 2013]; this is similar to intubating conditions achieved with rocuronium 0.6 mg·kg⁻¹ [Sparr et al 1996]. Sevoflurane 8 Vol% combined with remifentanil 2.0 µg·kg⁻¹ caused a significant reduction of mean arterial pressure. This technique, however, was used in young ambulatory patients (median age 16 and 18 years); therefore, the hypotension was not of clinical importance in the study [Cagiran et al 2013].

In addition, multiple studies have documented that the avoidance of neuromuscular blockade increases the risk of difficult tracheal intubation and difficult mask ventilation.

*We partly agree with the reviewer and added the following paragraph:*

Avoidance of neuromuscular blockade may increase the risk of difficult tracheal intubation; moreover, it may increase the risk of difficult mask ventilation [Lundstrom et al 2009, Warters et al 2011]. In a Danish observational study 5.1 % of 103,812 patients had a difficult tracheal intubation; avoiding neuromuscular blockade was one risk factor in the multivariate analysis (odds ratio 1.48) [Lundstrom et al 2009]. Neuromuscular blockade with rocuronium improved significantly mask ventilation compared with saline; in all 42 patients with rocuronium, ventilation was possible by mask [Warters et al 2011]. In an observational study of 53041 patients with an attempt for mask ventilation, however, from the 77 patients (0.15 %) with impossible mask ventilation, 73 patients received a neuromuscular blocking drug during management of the airway;
neuromuscular blockade did not improve mask ventilation [Kheterpal et al. 2009]. In this study neck radiation changes represented the most significant risk factor for impossible mask ventilation [Kheterpal et al. 2009]. Difficult mask ventilation combined with difficult laryngoscopy was observed in 698 patients (0.40 %) from 176,679 patients [Kheterpal et al 2013]. Independent risk factors for difficult mask ventilation combined with difficult laryngoscopy were neck radiation changes, presence of teeth, Mallampati III or IV and male sex among 12 independent predictors; the impact of neuromuscular blocking agents could not be assessed [Kheterpal et al 2013].

As authors correctly point out, acceptable conditions may be achieved with IV alfentanil/remifentanil and propofol only, if avoidance of NMB is desired. In that regard, doses of remifentanil 4 mcg/kg are not usually required to produce acceptable conditions for intubation under propofol anesthesia; 2-3 mcg/kg is usually sufficient.

*We partly agree with the reviewer and added the following sentences:*

Remifentanil in doses of 1.0 to 4.0 µg·kg⁻¹ combined with propofol provided excellent and good (acceptable) intubating conditions in many studies [Bouvet et al 2009, Stevens et al 1998, Erhan et al 2003, Stefanutto et al 2012]. In one study, remifentanil 2 µg·kg⁻¹ and propofol 2.0 mg·kg⁻¹ were sufficient to reach in 11 from 12 healthy volunteers excellent intubating conditions [Stefanutto et al 2012]. Remifentanil and propofol were given over 5 to 10 seconds, and propofol was administered immediately after the remifentanil bolus; this is applicable with healthy volunteers or young healthy patients, but this technique is not applicable for patients with ASA grade II or III. Some studies showed that doses as high as 4.0 µg·kg⁻¹ were necessary to obtain excellent intubating conditions [Woods et al 2005]. Doses of remifentanil ≥ 2 µg·kg⁻¹ were mainly associated
with arterial hypotension and bradycardia; hence, this induction technique is not suitable for old patients or for patients with cardiovascular diseases [Woods et al 2005]. In a observational study the authors studied a flexible approach using neuromuscular blocking agents or not; the use of the neuromuscular blocking agent depended on the decision of the anesthesiologist [Baillard et al 2005]. Clinically acceptable intubating conditions were found in 98.2 % of the patients in the relaxant-free intubating group; post-intubation laryngeal symptoms like sore throat and dysphonia were comparable between groups. In the relaxant-free intubating group propofol was used with a dosage of 3.64 mg·kg⁻¹ (median), supplemented with sufentanil [Baillard et al 2005]. Arterial hypotension was observed in 14 % of the patients, but not increased in the relaxant-free group compared with the relaxant group. The patients in the relaxant-free group, however, were significantly younger and in a better ASA physical grade [Baillard et al 2005].

The authors may wish to review the following references:

We want to thank the reviewer for the proposed references; we used some of them in the discussion (see above).
Reviewer #2

General Comments:
The study compares tracheal intubation conditions and side effects after using one of two induction techniques; either propofol, remifentanil, and sevoflurane versus propofol, remifentanil, and rocuronium. It is no surprise to find better intubation condition when the muscle relaxant was used.

*We hypothesized that sevoflurane 1.0 MAC is sufficient to provide clinically acceptable intubating conditions, when sevoflurane is combined with a standard anaesthesia induction with propofol and a continuous infusion of remifentanil. The subscore Vocal Cords, however, was comparable between groups; postoperative hoarseness and vocal cord injuries were comparable, too. Maybe, the concentration of sevoflurane was insufficient; this could be studied in the future.*

Specific Comments:
Abstract:
Please rephrase conclusions: Change to “Overall intubating conditions were better when rocuronium was used. Side effects were similar in both groups.

*We agree with the reviewer and changed the conclusions; we changed the next words and next phrases, as proposed by the reviewer, too.*

Conclusions: Overall intubating conditions were better, when rocuronium was used; the subscore vocal cords was comparable. Side effects were similar in both groups.

Introduction:
1- P4 L4-5: please add the reference after vocal cord injuries

*Poor intubating conditions are associated with more vocal cord injuries [Mencke et al 2003]; therefore, the aim is to achieve good and excellent, summarized as clinically acceptable, intubating conditions.*
The SEVO (sevoflurane) group received propofol, remifentanil and sevoflurane 1.0 MAC; the MR (muscle relaxant) group received propofol, remifentanil and rocuronium 0.45 mg·kg\(^{-1}\). The primary outcome measure was the intubating score assessed during tracheal intubation [10]. Secondary outcome measures were the MAP, the heart rate (HR) and bispectral index (BIS); in addition, we assessed the incidence and severity of vocal cord injuries at 24 hours after surgery (assessed by videolaryngoscopy), the incidence and severity of hoarseness and the incidence and severity of sore throat up to 72 hours after surgery.

Methods:
1- Page 6 : Change surgery of the ear to ear surgery

Eligible patients included adults aged 18-80 years, American Society of Anesthesiologist (ASA) grade I-III, which were undergoing orotracheal intubation for ear surgery.

2- Page 6: Please delete Cormack grade 3: This is a laryngeal view classification that can only be assessed with direct laryngoscopy (after induction)

This is right; patients were excluded from analysis, when Cormack grade was 3 or 4 (please see Figure 1). We wanted to assess intubating conditions and vocal cord injuries; therefore, we wanted to include only patients, where we could see vocal cords (Cormack I and II.

Exclusion criteria were a known or suspected difficult airway, such as mouth opening <
3.5 cm or Mallampati score 4 or Cormack grade 3 and 4; an allergy against the anaesthetics;

Figure 1 Flow chart of patient distribution.
3- Page 6: please delete allergy to anesthetics

Exclusion criteria were a known or suspected difficult airway, such as mouth opening < 3.5 cm or Mallampati score 4 or Cormack grade 3 and 4;

4- Change randomization to randomization

We used throughout British English spelling; therefore we wrote randomisation. We can change the spelling in the entire manuscript; let us know and we will change it.

5- Page 7 L 7: change than to when

We used the neuromuscular monitoring to have maximum neuromuscular block at time of tracheal intubation in the MR group; maximum neuromuscular block was achieved, when the TOF counts disappeared.

6- Page 8: Please explain how was the subject kept anesthetized from the time rocuronium was given until full relaxation

Maintenance of anaesthesia was performed with propofol 4.0 – 6.0 mg·kg·h⁻¹ and remifentanil 0.20-0.30 µg·kg·min⁻¹ in both groups. When a decrease of 20 % of the systolic pressure or a decrease below 100 mmHg or both was measured, ephedrine 5-10 mg IV was administered. Doses of ephedrine were recorded. Atropine IV was, when the HR decreased below 45 b·min⁻¹. At the end of anaesthesia patients’s tracheas were extubated. Patients were moved to the postanaesthesia care unit (PACU).

Results:
P 11 L 10: I could not understand starting from intubation conditions in the patients...(P of 0.06 is non significsnt). Please rephrase
Overall intubating conditions in the patients of the MR group were not significantly better compared with the patients of the SEVO group (p = 0.06); clinically acceptable intubating conditions (excellent and good conditions together), however, were significantly increased (p=0.03; Figure 2).

Discussion:
1- P 13 L 15: change worser to worse, change than to when

Intubating conditions, however, are worse, when NMBAs are omitted; difficult intubation is more common [17].

2- In the conclusion, please spell out the superiority of the muscle relaxant induction technique regarding intubation conditions

We showed that intubating conditions with propofol 1.5 mg·kg\(^{-1}\), remifentanil 0.30 µg·kg\(^{-1}\)·min\(^{-1}\) and sevoflurane 1.0 MAC - instead of rocuronium 0.45 mg·kg\(^{-1}\) - were clinically acceptable in 82% of the patients; intubating conditions, however, were better, when rocuronium was used. MAP decreased significantly compared to baseline values, but with no difference between the study groups. The incidence and severity of vocal cord injuries in patients receiving sevoflurane instead of a muscle relaxant was similar to those receiving rocuronium.
Reviewer #3

Major Compulsory Revisions
It seems extubation criteria are not defined or standardized. Please indicate in the manuscript why you scored extubation criteria.

To clarify, we changed the sentence in the Methods` section.

At the end of anaesthesia patients`s tracheas were extubated, when the patients opened their eyes or began to cough or both. Afterwards, patients were moved to the postanaesthesia care unit (PACU).

We added in the Discussion` s section, why we scored extubating conditions.

Vocal cord injuries may occur during tracheal intubation, during surgery and at the end of anaesthesia, when the tube is removed. Therefore, we assessed not only intubating conditions, but also extubating conditions to reveal possible risk factors for vocal cord injuries. The duration of anaesthesia was significantly longer in the MR compared to the SEVO group.

Please explain how you analyzed the 2 patients that needed muscle relaxation for tracheal intubation.

Tracheal intubation was possible in all patients. In two patients from the SEVO group, however, tracheal intubation was only possible after administration of rocuronium (see Figure 1). Vocal cords were closed and did not open after propofol 30 mg IV; to avoid vocal cord injuries, rocuronium 0.45 mg·kg⁻¹ was applied.
Figure 1 Flow chart of patient distribution.