Evaluation of Remifentanil-Propofol Infusion for Short-Term Laryngoscopic Surgery

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Summary

Purpose:
This study aimed to assess the conditions provided by remifentanil and propofol during short-term laryngoscopic surgery.

Methods:
Twenty-two patients, ASA I and II, were studied. Anesthesia was induced with remifentanil 5µg•kg^{-1} and propofol 2.5mg•kg^{-1} administered over a period of 2min.

Results:
The conditions for laryngoscopic surgery were excellent in 21 out of 22 patients (96%). Based on a predefined 20% equivalence margin remifentanil-propofol infusion was equivalent to a fictitious anesthetic technique which provides

optimum conditions ($p < .05$). Bradycardia and hypotension required treatment in 18% and 41% of the patients, respectively.

Conclusions:
The combination of remifentanil $5\mu g \bullet kg^{-1}$ and propofol $2.5mg \bullet kg^{-1}$ provides excellent conditions for short surgical procedures on the vocal cords and may be an alternative to any anesthetic technique which provides optimal conditions for laryngoscopic surgery. However, the observed rate of bradycardia and hypotension may limit the use of this technique to patients with normal cardiovascular reserve.

Key words:
Laryngoscopy, remifentanil, propofol, anesthesia, vocal cord

Überprüfung der Eignung einer Remifentanil-Propofol-Infusion bei laryngoskopischen Kurzeingriffen

Zusammenfassung

Rationale:
Es sollten die durch eine Kombination aus Remifentanil und Propofol erzielbaren Bedingungen für laryngoskopische Kurzeingriffe überprüft werden.

Methoden:
Zweiundzwanzig Patienten, ASA I und II, erfüllten die Studienkriterien. Die Anästhesie wurde mit einer zweiminütigen Verabreichung von Remifentanil (5µg/kgKG) und Propofol (2,5mg/kgKG) eingeleitet.

Ergebnisse:
Die Bedingungen für den laryngoskopischen Eingriff waren bei 21 der 22 Patienten (96%) ausgezeichnet. Auf der Basis eines prospektiv festgelegten Äquivalenzrahmens von 20% war die Gleichwertigkeit des Remifentanil-Propofol-Regimes mit einem fiktiven Anästhesieregime mit optimalen Eigenschaften nachweisbar ($p < 0,05$). Bradykardie und Hypotonie waren bei 18% bzw. 41% der Patienten behandlungsbedürftig.

Schlussfolgerungen:
Die Kombination von Remifentanil (5µg/kgKG) und Propofol (2,5mg/kgKG) schafft ausgezeichnete Bedingungen für Kurzeingriffe an den Stimmbändern und könnte eine Alternative zu anderen Anästhesieregimen, die optimale

Eingriffskonditionen bieten, darstellen. Allerdings spricht die beobachtete Rate von Puls- und Blutdruckabfällen für eine Beschränkung der Anwendung dieses Regimes auf Patienten mit normaler kardiovaskulärer Reserve.

Schlüsselwörter:
Laryngoskopie, Remifentanil, Propofol, Anästhesie, Stimmband

Introduction

In ambulatory surgery short procedures on the vocal cords, e.g. biopsies or polypectomies are usually done using direct laryngoscopy. It is essential for the surgeon to find the vocal cords both optimally open and immobile. The anesthetist has to provide a secure airway, to maintain normal oxygenation during the period of no ventilation, and to ensure rapid awakening of the patient.

Due to the very fast onset of and fast recovery from succinylcholine, an anesthetic technique including this drug is ideal for short diagnostic procedures on the vocal cords. Smooth conditions for laryngoscopic surgery develop within 60 seconds after administration of succinylcholine and, unlike with a non-depolarizing muscle relaxant, they do not depend on an adequate depth of anesthesia [1,2]. However, the potential side effects of this drug, especially the triggering of malignant hyperthermia, can be extremely serious [3].

Anesthetic techniques using propofol in combination with different doses of alfentanil or remifentanil provide excellent conditions for tracheal intubation in most patients [4-10]. The rate of excellent intubation conditions increased with the dose of the opioid administered [4,6,10]. Direct laryngoscopy was also studied without intubation in both children [11] and adults [12]. Remifentanil is the opioid with the shortest half-life and thus the best controllability [13,14]. This pharmacokinetic profile is combined with an excellent safety and tolerance [15].

These promising properties of opioids and especially of remifentanil in addition to experiences with the well-known side effects of succinylcholine were the trigger to change the anesthetic technique in our department some time ago. We eliminated succinylcholine from our regimen and switched to a combination of remifentanil and propofol. After dosage titration we found a new regimen which was from our subjective point of view safe and efficient. However, these impressions had to be objectified.

Therefore, the present study was performed to assess whether a regimen with a relatively high dose of remifentanil ($5\mu g \bullet kg^{-1}$) and propofol provides the same excellent conditions for short surgical procedures on the vocal cords as a regimen with the best possible properties.

Methods

General Design:

The study was designed as a prospective clinical trial (one-group design). Efficacy data from the study were compared to a postulated best-case scenario. This best-case scenario was defined as a situation which provides optimum results in any case (best-case model). The assumption of a best-case scenario as a control was taken only for the primary endpoint (conditions for laryngoscopic surgery). This best-case model was a very conservative approach because in clinical routine neither a succinylcholine regimen nor others really reach always excellent conditions. So on the one hand this comparison with a postulated best-case scenario caused a high level of demands for the new regimen but on the other hand prevented the allocation of patients to other regimens which were not used any more routinely in our department for safety reasons (especially succinylcholine regimen). The patient protection included furthermore a stopping rule (clear-cut stop criterion): The study had to be stopped when more than one evaluation of the conditions for laryngoscopic surgery showed a non-excellent result (failure to prove equivalence of the remifentanil-propofol regimen and a fictitious anesthetic technique which provides optimum conditions).

However, the chosen design involves some bias potential. So, it was not possible to blind any member of the study group (no possibility of observer-blinding). As a counter-measure the conditions for laryngoscopic surgery were documented by video and the video tape was rated by an external expert not being involved in the study and blinded to the primary rating results. This expert had the competence to overrule the on-site rating. As already mentioned above, a second limit of the design is the fact that to a certainty no regimen produces always perfect conditions for laryngoscopic surgery. This means that the comparison of the remifentanil-propofol regimen with a best case situation is not completely transferable into a comparison with a concrete alternative regimen. Of course, also no safety and tolerance comparisons can be performed. Furthermore, it has to be considered that the chosen equivalence margin allows a 20% deviation from optimal conditions for laryngoscopic surgery. This relatively wide range was a consequence of the limited sample size. So, from a clinical point of view, the study although designed as a proof of equivalence bears a meaning of a pilot

study. However, it should be mentioned that comparisons with postulated best-case scenarios are not unusual in many fields of medicine like diagnostics (100% organ function), epidemiology and outcome evaluation (100% survival, recovery or prevention).

Patients and Methods:

All study procedures strictly adhered to national law and to the ethical standards of the Declaration of Helsinki (amended in Edinburgh 2000). Upon approval by the Ethics Committee adult patients fulfilling the following inclusion criteria were enrolled: informed consent, indication for short vocal cord surgery, ASA I to II, body mass index >15 and <35kg•m^{-2}, age >19 and <70 years.

Patients were premedicated with midazolam 0.1mg•kg^{-1} given orally 60min before anesthesia. Once in the operating room, intravenous access was established by inserting an 18-gauge cannula into an antebrachial vein and monitoring of electrocardiogram (ECG), heart rate (HR), peripheral arterial hemoglobin oxygen saturation (SpO2) as well as of systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP) was commenced. After 3min of preoxygenation anesthesia was induced with propofol 2.5mg•kg^{-1} and remifentanil 5µg•kg^{-1} administered simultaneously over a period of 2min via two separate infusion pumps (Alaris IVAC PCAM 5001-03992, Alaris Medical Systems, Germany). Once the patients became unconscious, ease of ventilation via face mask was rated as easy (=1), satisfactory (=2) or impossible (=3).

Surgery began 60sec after the end of infusion. At this time ventilation via face mask was discontinued at the longest until peripheral oxygen saturation (SpO_2) dropped below 90%. Within this time interval the operation should have been completed. Whenever this was not the case, the operation was interrupted for 1min to allow for oxygen ventilation via face mask and the simultaneous administration of propofol 1mg•kg^{-1}.

Conditions during laryngoscopic surgery were evaluated by the same surgeon in all patients according to a modified standard scheme adapted from Viby-Mogensen [16] (Table 1), which is based on the assessment of ease of laryngoscopy, position and movement of vocal cords, as well as coughing and limb movement during laryngoscopy and the surgical procedure, respectively. The scoring “excellent“ is only possible when all sub-scorings have the best expression. The scoring “good“ is only possible when no sub-scoring has the worst expression.

Table 1
Conditions for laryngoscopic surgery (adapted from [16])

	Conditions for laryngoscopic surgery		
	Clinically acceptable		**Clinically not acceptable**
	Excellent	**Good**	**Poor**
Laryngoscopy	Easy	Fair	Difficult
Vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Response to laryngoscopic surgery			
Movement of limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	Sustained (>10sec)

The condition (position, movement) of the vocal cords in the period 2-5sec before and after the intervention was recorded on video. Upon completion of the medication phase the collected video tapes were evaluated by a surgeon not involved in the study. This rating was set against the original scoring and the conformity of both ratings was recorded. This control measure was planned preferentially for all interventions but at least for spot-check.

Finally, the time until return of spontaneous ventilation (at least 8 breaths/min ascertained by the observation of chest excursions and the reservoir bag) and awakening (eye opening) of the patients was documented. During the entire study period all adverse events were documented and analyzed in an effort to detect possible side effects of the investigated treatment regimen. In patients developing hypotension (SAP <90mm Hg) ephedrine 10mg was administered and bradycardia (HR <50/min) was treated with atropine 0.5mg.

Statistical Analysis

For the primary endpoint (conditions for laryngoscopic surgery) only two opposed scorings were taken: “excellent” and “not excellent” (irrespective of whether good or poor). Equivalence was tested using a one-tailed confidence interval CI (significance level: 95%) for proportions of a binomial distribution – therefore the equivalence margin was 80% to 100%. Equivalence was given when the lower margin of the appropriate one-sided confidence interval for the primary endpoint lay within the equivalence margin. Due to the specific nature

of the primary endpoint, equivalence testing can also be performed on its sub-scores for the purpose of confirmation (equivalence of the primary endpoint = equivalence of all sub-scores). The complete statistical analysis was performed by the use of the SPSS software package 10.0 (SPSS Inc, Chigago, IL, USA). Unless otherwise mentioned descriptive data in the text are means (standard deviations and minimum - maximum are put in parenthesis).

Results

Twenty four patients were enrolled into the study, 22 of them fulfilled all study criteria and were defined as valid cases for efficacy (demographic and surgical data see Tables 2 and 3). The data of 2 patients had to be excluded because of major protocol violations. One patient was too old and the other patient received a dose of remifentanil that was definitely too low.

Table 2
Demographics and surgery characteristics

Patients (n)	22
Age (yr)	51 (19 – 66)
Height (cm)	169 (152 – 187)
Weight (kg)	69 (53 – 89)
Body mass index (kg $\bullet m^{-2}$)	24.7 (19.0 – 28.4)
Sex (n male / n female)	11 / 11
Duration of surgical procedure (min)	3.00 (2.00 – 6.00)

metric variables: medians, minimum – maximum in parenthesis

Table 3
Indications for surgical procedure (n)

Vocal cord tumor	8
Tachyphonia	8
Leucoplacia	6

Primary intervention was successful in all 22 cases. No secondary intervention was necessary. Intubation conditions were rated as clinically acceptable in all patients (100%; one-sided lower boundary CI: 87%) and excellent in 21 out of 22 patients (96%; one-sided lower boundary CI: 80%). Based on the defined equivalence margin of 80% to 100% the investigated treatment regimen (remifentanil and propofol) was equivalent to a fictitious treatment regimen based on predetermined optimal intubation conditions ($p < .05$). This equivalence is also true of all sub-scores (laryngoscopy, position and movement of vocal cords,

movement of the limbs and coughing as a reaction to surgical intervention). The only patient whose intubation conditions could not classified as excellent showed an intermediate position of immobile vocal cords and slight movement of the limbs. Unfortunately, 7 video tapes were not analyzable because of recording problems. The analysis of the 15 remaining video tapes with correct recordings by an independent surgeon confirmed all primary ratings (Table 4).

Table 4
Laryngoscopic assessment of vocal cords

	Assessment by surgeon during laryngoscopic surgery (n=22)	**Video tape assessment** (n=15)
Vocal cord position		
abducted	21	14
intermediate	1	1
closed	0	0
Vocal cord movement		
none	22	15
moving	0	0
closing	0	0

Resumption of spontaneous ventilation was observed 7 min (SD 2.8 min, range 1 - 11min) after end of remifentanil-propofol infusion. The patients awakened 7min (SD 3.1min, range 1 - 13min) after end of remifentanil-propofol infusion.

Nine out of 22 patients (41%) required a single pharmacological intervention for low blood pressure with ephedrine 10mg and 4 patients (18%) for low heart rate with atropine 0.5mg (hemodynamic parameters see Table 5).

Table 5
Hemodynamic parameters

	-6	**-3**	**-1**	**1**	**End**	**Sp**	**Aw**
SAP (mmHg)	145 ± 19	138 ± 20	106 ± 20	104 ± 24	114 ± 19	117 ± 15	127 ± 18
DAP (mmHg)	88 ± 10	86 ± 10	59 ± 10	68 ± 18	72 ± 14	73 ± 12	78 ± 11
MAP (mmHg)	105 ± 14	103 ± 13	74 ± 13	80 ± 20	87 ± 15	87 ± 12	94 ± 13
HR (/min)	78 ± 15	80 ± 16	66 ± 14	62 ± 10	74 ± 12	75 ± 11	78 ± 15

means ± standard deviations
n (number of patients) = 22 for all calculations; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; HR = heart rate; -6 = 6 min before surgical intervention; -3 = 3 min before surgical intervention (= start of drug infusion); -1 = 1 min before surgical intervention (=end of drug infusion); 1 = 1 min after beginning of surgical intervention; End = end of surgical intervention; Sp = beginning of spontaneous breathing; Aw = awakening of the patient

There were no signs of opioid-induced muscle rigidity.

It is noteworthy that one of the two drop outs, namely the patient who received a dose of remifentanil ($4\mu g \bullet kg^{-1}$) that was definitely lower than the defined dose, had only good intubation conditions. The other drop out, namely the patient who was too old, had excellent intubation conditions.

Discussion

Surgical intervention on the vocal cords requires both optimal visibility and immobility. Avoiding succinylcholine for planned procedures on the vocal cords might prevent patients from possible side effects associated with this drug. In the present study we investigated a succinylcholine-free anesthetic regimen (a combination of remifentanil and propofol) which has been introduced into the clinical routine of our department some time ago during short-term laryngoscopic surgery. The study results demonstrate that remifentanil $5\mu g \bullet kg^{-1}$ and propofol $2.5mg \bullet kg^{-1}$ given over a period of 2min reliably provide excellent conditions for rigid laryngoscopy and laryngoscopic surgery. In previous studies intubation conditions after various doses of remifentanil, namely $2\mu g \bullet kg^{-1}$[17], $3\text{-}4\mu g \bullet kg^{-1}$[9], $4\mu g \bullet kg^{-1}$[4] and $4\text{-}5\mu g \bullet kg^{-1}$[10] were investigated. Even though differences in methodology do not allow an exact comparison of these studies, the percentage of excellent intubation conditions has been shown to grow with an increasing dose of remifentanil. Wiel et al. [12] used remifentanil $2\mu g \bullet kg^{-1}$ for purely diagnostic procedures on the vocal cords and reported abducted vocal cords in 24 out of 30 patients. The fact that remifentanil re-injections were required in 19 out of their 30 patients strongly supports the use of higher doses. In the current study we administered remifentanil $5\mu g \bullet kg^{-1}$, because we had frequently experienced unsatisfactory conditions for short surgical interventions on the vocal cords in clinical practice, when we had started out with lower doses (2 up to $4\mu g \bullet kg^{-1}$). The particular importance of a higher dosage was also confirmed by the observation that the dropped out patient who received only $4\mu g \bullet kg^{-1}$ of remifentanil did not show completely satisfactory conditions. However, when comparing different studies one must not forget that in the current study we examined the vocal cord conditions for surgical interventions, whereas the intubation studies with remifentanil also assessed the conditions during placement of the tube in the trachea which represents a stronger stimulus than laryngoscopy [18]. Propofol was used because it is superior to, for instance, barbiturates in decreasing muscle tone and abolishing laryngeal responses to tracheal intubation or laryngeal mask insertion [19,20].

Duration of apnea and return of spontaneous ventilation in our study were similar to the data presented by Heier et al. [1] and Hayes et al. [2], who used thiopental 5mg•kg^{-1} and succinylcholine 1mg•kg^{-1} for induction of anesthesia, and therefore adequate for this particular surgical procedure of short duration in an ambulatory setting.

Bradycardia, hypotension and muscle rigidity are the most common side effects associated with remifentanil [21]. The combination of remifentanil and propofol prevented the increase in heart rate and blood pressure following direct laryngoscopy and surgical intervention on the vocal cords. The rate of adverse hemodynamic side effects we observed is comparable to that incidence reported by Thompson et al. [22] who also designed their study without a concurrent anticholinergic agent. Such adverse hemodynamic side effects can be hazardous in hypovolemic or elderly patients or in patients with clinically relevant cardiovascular disease [8]. Sebel et al. [23] found that after remifentanil application decreases in arterial blood pressure and heart rate, 20% on average, were independent of the given dose which escalated from 2 to 30µg•kg^{-1}. The authors suggested that the absence of cardiovascular depression was possibly attributable to pretreatment with glycopyrrolate, which may have masked a dose-related effect. Opioid-induced muscle rigidity was not observed in our study, perhaps because of the rather moderate injection rate of remifentanil, pretreatment with midazolam [24] and the large dose of propofol.

Our technique may also be appropriate for surgical interventions on the upper respiratory tract in children. Klemola et al. [25] who used remifentanil 4µg•kg^{-1} in combination with propofol 3.5mg•kg^{-1} reported excellent to good conditions for tracheal intubation. In a study on microlaryngoscopy and bronchoscopy in young children, Thaung et al. [11] induced anesthesia with halothane and maintained it with propofol 12mg•kg^{-1}h^{-1}.

On the basis of the study results we conclude that remifentanil 5µg•kg^{-1} in combination with propofol 2.5mg•kg^{-1} given over a period of 2min provides good to excellent conditions for direct laryngoscopy in patients with a favorable airway anatomy and hence allows successful short time elective surgery on the vocal cords without administering a neuromuscular blocking drug. This technique represents an equivalent alternative to anesthetic regimens that include succinylcholine. The remifentanil-propofol combination successfully prevented any cardiovascular response to laryngoscopy. Remifentanil-propofol infusion may be especially suitable for ambulatory anesthesia because of the rapid resumption of spontaneous ventilation and fast recovery. However, it is doubtful

that this method is also appropriate for ASA III and IV patients, particularly in view of its potentially severe hemodynamic side effects.

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