Three Different Doses of Remifentanil in TIVA for Direct Laryngoscopy: A Comparison for Hemodynamic, Stress Responses and Recovery

Direkt Laringoskopide TİVA'da Remifentanil'in Üç Farklı Dozunun Hemodinami, Stres Yanıt ve Derlenme Açısından Karşılaştırılması

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Geliş Tarihi/*Received:* 14.08.2012
Kabul Tarihi/*Accepted:* 26.04.2013

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ABSTRACT Objective: The ideal anesthesia for direct laryngoscopy must be deep and short, the also recovery period should be fast. In this study, we aimed three different doses of remifentanil as a part of the total intravenous anesthesia (TIVA) during direct laryngoscopy in points of hemodynamic stability, stress responses and recovery characteristics. **Material and Methods:** After induction of anesthesia with remifentanil 1 μkg^{-1}, propofol 2 $mgkg^{-1}$ and succinylcholine 1 $mgkg^{-1}$, 64 patients randomly received remifentanil infusion doses 0.2, 0.3 or 0.4 $\mu kg^{-1}min^{-1}$ in combination with propofol 50 $\mu kg^{-1}min^{-1}$ and 50% $O_2 + N_2O$. Arterial pressures and heart rates were recorded at 3 minutes' intervals from the baseline. Remifentanil 1 μkg-1 was used for the attenuation of stress responses. Recovery times as well as Aldrete scores were assessed. **Results:** In the groups with remifentanil infusion rates of 0.2 $\mu kg^{-1}min^{-1}$ (12 patients required a total of 18 additional doses) and 0.3 $\mu kg^{-1}min^{-1}$ (8 patients required 13 additional doses), supplemental bolus doses of remifentanil were needed to suppress the acute hemodynamic and stress responses. No additional bolus dose of remifentanil was necessary in the 0.4 $\mu kg^{-1}min^{-1}$ group. Hypotensive periods were seen in the remifentanil 0.4 $\mu kg^{-1}min^{-1}$ group but those were in clinically acceptable limits. No differences were found in recovery times between groups. Aldrete recovery scores of 9 or 10 were obtained 5 minutes after the discontinuation of anesthetics in all groups. None of the patients complained of intraoperative recall. **Conclusion:** We conclude that 0.4 $\mu kg^{-1}min^{-1}$ infusion rate of remifentanil in combination with propofol during direct laryngoscophic procedures may provides hemodynamic stability.

Key Words: Remifentanil; laryngoscopy; hemodynamics; anesthesia recovery period; anesthesia, general

ÖZET Amaç: Direkt laringoskopi için ideal anestezi; derin ve kısa, derlenme periodu hızlı olmalıdır. Bu çalışmada; direkt laringoskopide total intravenöz anestezide (TİVA) yer alan remifentanilin üç farklı dozunun hemodinamik stabilite, stres yanıt ve derlenme özellikleri açısından karşılaştırılmasını amaçladık. **Gereç ve Yöntemler:** Remifentanil 1 μkg^{-1}, propofol 2 $mgkg^{-1}$ ve süksinilkolin 1 $mgkg^{-1}$ ile anestezi indüksiyonundan sonra, randomize olarak, 64 hastada remifentanil 0,2, 0,3 veya 0,4 $\mu kg^{-1}min^{-1}$ dozlarında, propofol 50 $\mu kg^{-1}min^{-1}$ ve %50 $O_2 + N_2O$ ile uygulandı. Arter basıncı ve kalp hızı bazal ölçümden itibaren 3 dakika aralıklarla kaydedildi. Stres yanıtlarda baskılamak için remifentanil 1 μkg^{-1} uygulandı. Derlenme zamanları ve Aldrete skorları değerlendirildi. **Bulgular:** Remifentanil 0,2 $\mu kg^{-1}min^{-1}$ (12 hastada 18 ek doz) ve 0,3 $\mu kg^{-1}min^{-1}$ (8 hastada13 doz) gruplarında hemodinamik ve stress yanıtlara ek remifentanil ihtiyacı olmuştur. Remifentanil 0,4 $\mu kg^{-1}min^{-1}$ grubunda ek remifentanil dozu gerekmemiştir. Hipotansif periyotlar, remifentanil 0,4 $\mu kg^{-1}min^{-1}$ grubunda gözlenmiştir, ancak klinik olarak kabul edilebilir sınırlardadır. Derlenme süreleri açısından gruplar arasında fark gözlenmemiştir. Aldrete derlenme skorları anestezi sonlandırılmasından 5 dakika sonra tüm gruplarda 9-10 şeklindedir. Hastalarda operasyon döneminde uyanıklık bulgusuna rastlanmamıştır. **Sonuç:** Sonuç olarak; direkt laringoskopide; 0,4 $\mu kg^{-1}min^{-1}$ infüzyon dozunda remifentanil propofol ile yeterli hemodinamik stabilite sağlanabilmektedir.

Anahtar Kelimeler: Remifentanil; laringoskopi; hemodinami; anestezi toparlanma dönemi; anestezi, genel

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Turkiye Klinikleri J Anest Reanim 2013;11(2):55-60

Direct laryngoscopy is stressful procedure. Excessive hemodynamic responses may occur, therefore profound analgesia is required. As it is also a short procedure, anesthesia is expected to be brief with fast and full recovery. Total intravenous anesthetic (TIVA) technique is often used usually with short acting opioids and hypnotic agents. Remifentanil has an outstanding therapeutic profile. Its rapid onset and offset of action with a context sensitive half life of 3-5 min and an elimination half life of about 10 min makes it superior to the other opioids for the attenuation of the brief but noxious stimuli.[1-4] However, escalation of the infusion dose is generally required to be able to stabilize the hemodynamic and to avoid bradycardia and hypotension.

In this study; three different infusion doses of remifentanil given in combination with propofol were compared in terms of the hemodynamic stability, stress responses and the recovery characteristics during direct laryngoscopic procedures.

MATERIAL AND METHODS

After approval by the Hospital Ethics Committe and obtaining written informed consents; 64 patients (ASA I-II, aged 18-70 years), presenting for diagnostic or therapeutic direct laryngoscopy were included in this study. Patients with uncontrolled hypertension (diastolic arterial pressure > 100 mmHg), sinus bradycardia (hearth rate < 50 beat min^{-1}), significant arrhythmias and ischemic heart disease, significant or uncontrolled organ dysfunction, those taking long term opioid medication or antihypertensive β blocker agents, morbidly obese patients and patients whose intubations were expected to be difficult, were not included into the study. Patients who presented any complication and who required a second dose of muscle relaxant were excluded from the study. The number of patients who had the history of diabetes mellitus, hypertension and chronic obstructive airway disease were listed in Table 1.

Premedication was not given. Patients were randomly allocated according to sealed envelopes to one of the three groups. Those in group I (n=21) were planned to receive 0.2 $\mu kg^{-1}min^{-1}$, group II (n=21); 0.3 $\mu kg^{-1}min^{-1}$, and group III (n=21); 0.4 $\mu kg^{-1}min^{-1}$ remifentanil infusion rates.

All patients had infusion of saline 5 $mLkg^{-1}hr^{-1}$ once they were in the operating room. Patients were monitored with electrocardiogram (ECG), noninvasive arterial pressure (systolic-SAP, diastolic-DAP and mean-MAP), heart rate (HR), peripheric oxygen saturation (SPO_2), and end tidal CO_2 (Nihon Kohden Life Scope-Japan). Study drugs were infused using infusion pumps (Flo-Gard 630-Baxter).

After the preoxygenation, anesthesia was induced with remifentanil 1 μkg^{-1} injected in 60 seconds, propofol 2 mg kg^{-1} was also given in 60 seconds followed by succinylcholine 1 mg kg^{-1} intravenously. After, orotracheal intubation (the internal diameter 6-6.5 mm) was performed direct laryngoscope was inserted. All groups were given propofol infusion at the rate of 50 μkg^{-1} min^{-1} and

TABLE 1: Demographic properties, duration of anaesthesia and surgery, history of chronic disease

Characteristics	Group I (n=21)	Group II (n=21)	Group III (n=21)
Age (Year)	47.2±10.4	46.6±11.4	51.3 ± 12.2
Weight (Kg)	78.7±12.7	77.6±14.0	71.6 ± 10.6
Gender (F/M)	3/18	8/13	2/19
Duration of Anaesthesia (min)	26.6±7.1	25.7±5.3	22.3±5.1
Duration of Surgery (min)	14.8±6.5	13.8±4.8	11.9±4.8
Co -diseases (Number of patients)			
Diabetes Mellitus	1	0	4
Hypertension	5	1	2
Chronic Obstructive Pulmonary Disease	16	15	12

50% O_2+N_2O besides remifentanil infusions for the maintenance of anesthesia. Soon after the induction of anesthesia, infusions of remifentanil and propofol were initiated. Ventilation was adjusted to maintain the $ETCO_2$ 30-40 mmHg. All patients had 1 $mgkg^{-1}$ methylprednisolone to attenuate postoperative laryngeal edema formation. The operation was performed by the same experienced surgeons.

Besides the demographic characteristics, duration of anesthesia and surgery were noted. Non-invasive SAP, DAP and MAP, heart rate, SPO_2 values were recorded before the induction (basal), after the induction, following intubation, at the start of surgery and at 3 minutes intervals until after the extubation. Hypertension (defined as a change in SAP >25% of baseline or >200 mmHg), tachycardia (HR >100 min^{-1}), somatic (extremity movements, eye opening, swallowing) and autonomic (lacrimation, sweating) responses were considered as inadequate analgesia and 1 μkg^{-1} bolus dose of remifentanil was given. The same bolus dose was repeated as required up to three times. Thereafter, remifentanil infusion rate was increased by 50% to maintain hemodynamic stability. Hypotension was defined as MAP < 60 mmHg. The infusion rate of saline was increased and increments of ephedrine 5 mg was given. Bradycardia (HR < 50 min^{-1}) was treated with intravenous atropine 1 mg.

At the end of the direct laryngoscopy, all anesthetic agents were discontinued. The total dose of propofol and remifentanil given to the patients were calculated. Times to spontaneous ventilation, sufficient breathing, extubation, response to the verbal comments as well as Aldrete recovery scores at postoperative 5^{th}, 10^{th}, and 15^{th} minutes were recorded. Side effects like muscle rigidity, shivering, nausea-vomiting were also noted. Patients were asked for intraoperative awareness after 4 hours postoperatively.

Sample number determined with 0.80 Power for α: 0.05 was established to be 21 when we considered delta value as 7 for average artery pressure parameter and as 8 for standard deviation parameter following power analysis applied on the initial group in the study.

During the evaluation of the results obtained from the study, NCSS 2007 & PASS 2008 Statistical Software (Utah, USA) program was used for statistical analysis. During the evaluation of the study data, student t test was used for the intergroup comparisons of descriptive statistical methods (Mean, Standard deviation) in addition to parameters with normal distribution and Mann Whitney U test was used for the intergroup comparisons of parameters without normal distribution. Paired sample t test was used for in-group comparison of parameters with normal distribution. Chi-Square test and Fisher Exact Chi-Square test were used for comparison of qualitative data. Results were evaluated at 95% confidence interval and a significance level of $p<0.05$.

RESULTS

The patient characteristics and the durations of anesthesia and surgery did not differ among groups (Table 1).

There were no significant differences between the groups with respect to the SAP and HR. Compared to the baseline values, the decrease in SAP were statistically significant within the groups after anesthesia induction, after intubation, at 3 minutes intervals ($p<0.01$) and extubation ($p<0.05$) (Figure 1). HR decrease was also significant after the beginning of surgery and 3 minutes intervals in group I, and after induction, after intubation, at 3 minutes intervals in group II ($p<0.01$) (Figure 2).

Stress responses like hypertension, tachycardia, grimacing and sweating were not seen in any of the patients. Extremity movements were similar among groups ($p=0.005$). Swallowing showed no difference among groups. None of the patients needed any supplemental dose of remifentanil in group III. The difference in the number of the bolus doses in group I and II were statistically significant compared to group III ($p=0.018$) (Table 2).

Frequency of bradycardia was similar among groups. Frequency of hypotension was significantly high in group III ($p=0.043$) and responded to the fluid resuscitation ($p<0.05$). Regarding the number of patients needed atropine, there was no difference among groups ($p=0.923$) (Table 3).

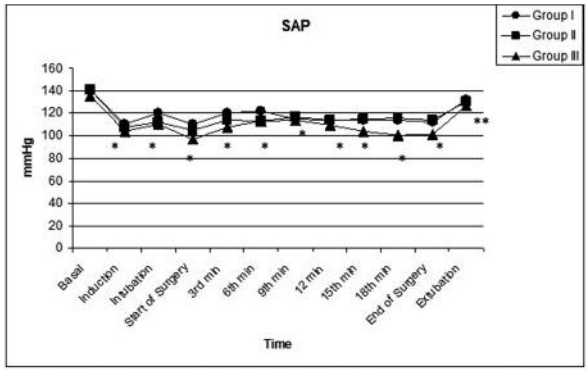

FIGURE 1: Systolic arterial pressure (SAP).

* p<0.01, ** p< 0.05 in group I, II, III compared basal values.

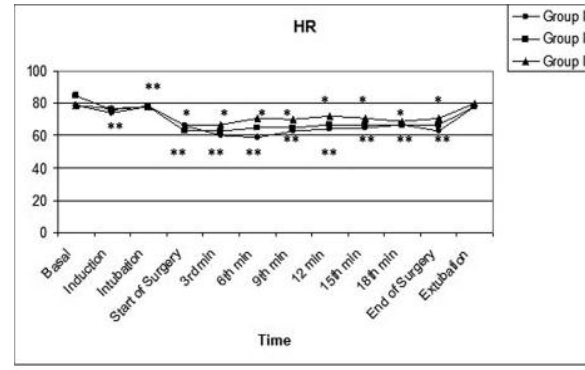

FIGURE 2: Heart rates (HR) values.

* p<0.01 in group I compared basal value, ** p<0.01 in group II compared basal value.

TABLE 2: Perioperative stress responses and supplemental / total dose of remifentanil, total dose of propofol.

		Group I n (%)	Group II n (%)	Group III n (%)	◆p
Perioperative stress responses	Hypertension	-	-	-	-
	Tachycardia	-	-	-	-
	Extremity movements	12 (57.1%)	7 (33.3%)	*2 (9.5%)	0.005
	Swallowing	0 (0.0%)	1 (4.8%)	0 (0.0%)	-
	Grimacing	-		-	-
	Sweating	-		-	-
Perioperative supplemental dose of remifentanil	1st bolus dose	7	5	**0 (0.0%)	0.018
	2nd bolus dose	4	1	0 (0.0%)	0.059
	3rd bolus dose + increase 50% infusion rate	1	2	0 (0.0%)	0.350
Total dose of remifentanil(µg) (Mean ± SD)		566.6 ± 40.2	739.2± 45.4+	710.2 ± 45.4++	0.0126
Total dose of propofol(mg) (Mean ± SD)		272.3 ± 20.8	255.2 ± 19.8	237.5 ± 21.2	0.0470

◆: Ki square test ,* Group I compared, Group III, ** Group I and II compared Group III + Group I compared, Group II, ++ Group I compared Group III

TABLE 3: Side effects and atropine bolus doses.

		Group I n (%)	Group II n (%)	Group III n (%)	◆p
Side effects	Bradycardia	5 (23.8%)	7 (33.3%)	6 (28.5%)	0.792
	Hypotension	0	0	3 (14.2%)	0.043*
	Muscle rigidity	-	-	-	-
	Awareness	-	-	-	-
Atropine bolus doses	1st bolus dose	5 (23.8%)	6 (28.5%)	6 (28.5%)	0.923
	2nd bolus dose	0	1 (4.8%)	2 (9.5%)	0.350

◆ : Ki square test

* Group III compared Group I and II

In three cases, the replacement of the laryngoscope was delayed. Some difficulty in mouth opening occurred in these cases. Single bolus dose of remifentanil was given to these patients. In one of them, an additional muscle relaxant had to be given, this patient was excluded from the study.

TABLE 4: Recovery times.

	Group I	Group II	Group III	*p
Spontaneous breathing time (minute)	4.4±1.7	4.4±2.1	5.47±1.5	0.1057
Adequate respiration time (minute)	5.4±1.8	5.5±2.1	6.1±1.5	0.1057
Extubation time (minute)	5.6±1.8	5.8±2.1	6.5±1.5	1.000
Verbal response time (minute)	5.4±1.8	5.6±2.1	6.1±1.5	0.1825
Aldrete score at 5th min	9.7±0.4	9.7±0.7	9.7±0.7	0.317

* Student t test

No differences were found in recovery times between groups. Aldrete recovery scores of 9 or 10 were obtained 5 minutes after the discontinuation of anesthetics in all groups (Table 4). None of the patients complained of intraoperative recall.

DISCUSSION

The primary end point of this study was achieving a hemodynamically stable patient with optimal control of intraoperative responses and with minimal side effects. Compared to the remifentanil infusion rates of 0.2; 0.3 $\mu kg^{-1}min^{-1}$, the rate of 0.4 $\mu kg^{-1}min^{-1}$ was more successful in terms of the suppression of somatic responses to intraoperative stimulations, and the number of the supplemental remifentanil bolus doses and infusion rate adjustments were less in this group. Although the occurance of hypotensive periods were more with this dosage, the fall of systolic blood pressure was within the clinically acceptable range.

The number of bradycardic episodes necessitating intervention were not low in groups (23.8%, 33.3%, 28.5%). In order to avoid the additive cardiac depressive effects of β blockers with the drugs used in the study, we excluded the patients who use hemodynamic change medications. Although we preferred to use anticholinergic agents symptomatically to observe the hemodynamic changes, premedication with an anticholinergic agent can be used when the hypotensive and bradycardic effects are to be avoided.[5]

The infusion rate of propofol used in this study (50 $\mu kg^{-1}min^{-1}$) was less than that normally used for maintenance of anesthesia for TIVA.[6,7] Propofol has many cardiovascular effects including hypotension.[8-12] The relatively high number of the elderly patients in the study population (42 patients over 55 years of age), led us to choose this relatively low infusion rates. The percentage of decrease in SAP was between 14.3-28.5% in all groups throughout the study which was a clinically acceptable magnitude of reduction. A concern with the use of smaller propofol doses is the potential for intraoperative recall. This frequency of recall is reported to be about 1-1.5% in the previous similar studies and the recommended lowest dose of propofol infusion is suggested as $^{-}75\ \mu\ kg^{-1}min^{1}$ without using nitrous oxide.[13] None of our patients complained about intraoperative awareness on enquiry, the addition of N_2O and the shortness of the operation might have played a role on this result.

Remifentanil infusion rates given for the anesthesia of upper airway procedures are generally higher than the one used in this study. Nillson et al. used 0.5 $\mu kg^{-1}min^{-1}$ remifentanil and 100 $\mu kg^{-1}min^{-1}$ propofol infusion rates and reported a completely abolished overall stress response to direct laryngoscopy and surgery, but at the expense of an increased incidence of hypotension and bradycardia as well as a slightly prolonged recovery time.[14] Hadimioglu et al. used 0.1 $\mu kg^{-1}min^{-1}$, 0.25 $\mu kg^{-1}min^{-1}$, 0.5 $\mu kg^{-1}min^{-1}$ remifentanil and 100 $\mu kg^{-1}min^{-1}$ propofol infusion rates for the abdominal surgery. They observed an increase of hypotension and longer recovery time in the 0.5 $\mu kg^{-1}min^{-1}$ remifentanil infusion rate group.[15] In these studies, propofol infusion rates were doubled when compared with our study; we think that this was the reason for than increased hypotension risk in the both other studies.

Prakash et al. studied remifentanil 1 μ kg^{-1} for induction followed by infusion of 0.5 $\mu kg^{-1}min^{-1}$ and showed attenuated hemodynamic responses to rigid bronchoscopy. Hypotension and bradycardia rates were not high in their patients, explained by the sympathetic stimulation during the procedure which was significantly short compared to ours. They concluded that lower doses of remifentanil might have been equally effective while producing less hypotension.[16]

Clinical adverse effects like muscle rigidity (0,8%) and respiratory depression can be seen after the bolus dose of remifentanil.[17] We therefore administered the bolus injection in 60 seconds, no patients had muscle rigidity. Postoperative nausea and vomiting (12-47% and 3-33%) are expected to increase after remifentanil as well as the other opioids. Nevertheless, propofol decreases this incidence when used in combination with remifentanil.[18] We did not observe any nausea and vomiting in our patients. Early recovery was observed similarly in all groups. Remifentanil offers a clinically important advantage with respect to an earlier return of cognitive functions, regardless of the infusion rate or duration.[19] Because propofol becomes the drug whose pharmacokinetics limit the rate of recovery when combined with remifentanil, we preferred reducing the propofol concentration and using remifentanil rescue doses to accelerate the recovery. Patients were generally alert, fully cooperated and satisfied when transferring to the post anesthesia room.

CONCLUSION

Remifentanil 1 μkg^{-1} IV as a bolus followed by an infusion 0.4 $\mu kg^{-1}min^{-1}$ effectively controlled hemodynamic, somatic and autonomic stress responses to direct laryngoscopy and did not cause any side effect when used in combination with 50 $\mu kg^{-1}\,min^{-1}$ dose propofol. The recovery times were fast in all groups. 0.4 $\mu kg^{-1}min^{-1}$ infusion rate of remifentanil is reliable for direct laryngoscopy.

Acknowledgement

Thanks to Emire Bor for her support in statistical analysis.

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