Hemodynamic effects, recovery profiles, and costs of remifentanil-based anesthesia with propofol or desflurane for septorhinoplasty

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ABSTRACT

Objectives: To compare hemodynamics, recovery profiles, postoperative side effects and costs of desflurane-remifentanil and propofol-remifentanil anesthesia for septorhinoplasty operations.

Methods: A prospective and randomized study was carried out at the Gazi University Hospital, Ankara, Turkey from April to September 2003. Forty patients undergoing septorhinoplasty operations were randomly allocated to receive desflurane-remifentanil (Group DES-REM) or total intravenous anesthesia (TIVA) (Group TIVA). Anesthesia was induced in both groups with remifentanil 1 $\mu g.kg^{-1}$, propofol 2-2.5 $mg.kg^{-1}$ and pancuronium 0.1 $mg.kg^{-1}$. Maintenance was achieved with O_2 50% in air at 4 $L.min^{-1}$ and infusion of remifentanil 0.1 $\mu g.kg^{-1}.min^{-1}$ in both groups. Group DES-REM received desflurane at 1 minimum alveolar concentration and Group TIVA received 10-4 $mg.kg^{-1}.hour^{-1}$ of propofol. Propofol infusion and desflurane were discontinued with the last surgical stitches, but remifentanil infusion continued in both groups until the nose was covered with plaster. Hemodynamic variables were recorded during the operation and one hour postoperatively in 5 min intervals. We recorded time of extubation, spontaneous eye opening and response to verbal commands times, visual analog scale pain scores, postoperative nausea and vomiting and Aldrete Recovery Score. Drug dosages and costs of each technique were determined.

Results: There were no statistically significant differences between the groups with respect to hemodynamic parameters, recovery profile, adverse effects, Aldrete Recovery Score and cost analysis. Visual analog scale at 5 min postoperatively was higher in group desflurane-remifentanil compared to group propofol-remifentanil ($p<0.05$).

Conclusion: Both desflurane-remifentanil and TIVA provide perioperative hemodynamic stability, early and easy recovery with similar cost profiles for septorhinoplasty operations.

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Septorhinoplasty operations are usually performed under general anesthesia, although local anesthesia may also be preferred. A critical factor in the management of general anesthesia is to provide a relatively bloodless field to optimize visibility for the surgeon.[1] The ideal anesthetic technique for septorhinoplasty operations should have a rapid onset of intraoperative amnesia and analgesia while facilitating a short recovery period without side effects.[2] Of the short-acting anesthetic drugs, remifentanil, propofol and desflurane have improved the ability of providing safe and effective anesthesia with few side effects and rapid recovery.[3] Specifically, the advantages of intravenous anesthesia using propofol over inhalation anesthesia have been extensively discussed in numerous studies with opposing results. The introduction of less-soluble inhaled anesthetics, such as desflurane, has added a new dimension to recovery and fast-tracking by allowing more rapid recovery and earlier discharge.[4] However, desflurane is associated with increased cost and incidence of postoperative nausea and vomiting (PONV) compared to older inhaled anesthetics.[5,6] The aim of this study was to compare hemodynamics, recovery profiles, PONV and costs of anesthetic techniques comprising remifentanil with desflurane, versus TIVA with remifentanil and propofol for septorhinoplasty operations.

Methods. This study was carried out at the Gazi University Hospital, Ankara, Turkey from April to September 2003. With hospital ethics committee approval and informed consent, we recruited 40 American Society of Anesthesiologist (ASA) I-II patients aged 18-45 years undergoing elective

septorhinoplasty procedure. Exclusion criteria were cardiovascular, respiratory, renal, hepatic or metabolic diseases, history of malignant hyperthermia, adverse reaction to inhalation anesthetics or propofol, chronic exposure to opioids, benzodiazepines, α_2 adrenoreceptors and ß-blockers, hematological disorders, and refusal by the patient. Patients were randomly assigned according to a computer-generated random number table to receive one of the following 2 anesthetic techniques: general anesthesia using desflurane and remifentanil (Group DES-REM) or TIVA based on propofol and remifentanil (Group TIVA). Sedative premedication was not administered. Monitoring included measurement of arterial blood pressure [mean arterial pressure (MAP)], heart rate (HR) and oxygen saturation [pulse oximetry (SpO_2)] (Taema Artema MM206, Artema Medical AB Sundyberg, Sweden). Before the induction of anesthesia, all patients received 100% oxygen for 3 minutes and IV lactated Ringer's solution 5 mL.kg^{-1}. Induction of anesthesia was identical in both groups. Anesthesia was induced with a bolus dose of remifentanil 1 µg.kg^{-1} injected over 30-60 seconds and a continuous infusion of remifentanil was started simultaneously at a delivery rate of 0.1 µg.kg^{-1}.min^{-1}. Propofol was given for hypnosis, starting at a dose of 2 mg.kg^{-1} and titrated thereafter at 10 mg every 10 seconds until the patients were unresponsive to verbal commands. Patients received pancuronium 0.1 mg.kg^{-1} to facilitate endotracheal intubation. For maintenance of anesthesia patients were randomly assigned to one of 2 treatment groups: Group TIVA received a variable-rate propofol infusion started at 10 mg.kg^{-1}.hour^{-1} and then titrated up to 4 mg.kg^{-1}.hour^{-1} and Group DES-REM received desflurane at 1 MAC in combination with O_2 50% in air at 4 L.min^{-1}. Ventilation patterns were adjusted to keep end-tidal CO_2 ($EtCO_2$) between 35-40 mm Hg. In both groups, remifentanil was administered 0.1 µg.kg^{-1}.min^{-1}, and subsequently titrated as required by the hemodynamic response to surgical stimulation. Increase in MAP and/or HR 20% above preinduction baseline values or by clinical signs of light anesthesia such as lacrimation, flushing or sweating were treated by increasing, firstly, the desflurane concentration (up to 1.2 MAC) and secondly, by remifentanil (max.0.35 µg.kg^{-1}.min^{-1}) in DES-REM group or, in the TIVA group, by an increase firstly in propofol (max. 10 mg.kg^{-1}.hour^{-1}) and secondly in remifentanil (max.0.35 µg.kg^{-1}.min^{-1}). Excessive depth of anesthesia as judged by hypotension (MAP <20% of the preinduction baseline) and/or bradycardia (HR <40 bpm) was treated with IV fluids, followed by a 50% decrement in remifentanil infusion rate. In case of inadequate response, IV ephedrine or atropine was administered for hypotension or bradycardia subsequently. Propofol or desflurane were decreased only in response to hypotension which was resistant to replacement of intraoperative fluid losses or treatment of bradycardia. Propofol and desflurane were discontinued with the last surgical stitch, but remifentanil infusion maintained until the nose was covered with plaster in both groups. The times of discontinuation of the anesthetic agents were recorded. At the same time, lungs were manually ventilated with 100% oxygen with a fresh gas flow of 4 L.min^{-1} until spontaneous ventilation started. Neuromuscular block was reversed at the end of surgery with neostigmine 0.04 mg. kg^{-1} and atropine 0.01 mg.kg^{-1}. Spontaneous breathing was achieved and extubation was performed. Heart rate, MAP, SpO_2 and $EtCO_2$ were recorded at pre-induction (baseline), 1 minute after induction of anesthesia, 1 minute after intubation and subsequently at 5 minute intervals throughout the anesthesia and recovery periods. Desflurane was administered by Tec 6 plus vaporiser (Datex-Ohmeda, USA) and both of propofol and remifentanil infusions were delivered with an infusion pump (IVAC 770, San Diego, CA). The doses of all anesthetic drugs were recorded. Recovery times were determined at 1-min intervals from discontinuation of the maintenance anesthetics to awakening (such as opening eyes on verbal command), response to commands (squeezing observer's hand), extubation, and orientation to person, date, and place. After extubation, patients were directly transferred to postanesthesia care unit (PACU), where further recordings were carried out by an independent observer blind to the anesthetic regimen. Pain was documented using a VAS (0-10), PONV and other adverse side effects were also noticed. Pain (VAS >3) was treated with intramuscular (IM) 1 mg.kg^{-1} of meperidine. Postoperative nausea and vomiting was treated with IV 0.15 mg.kg^{-1} of metoclopramide. When patients showed stable hemodynamics, no complications from the surgical field, and the Aldrete Score[7] was 9, patients were discharged from the PACU. The cost of desflurane was calculated using the following formula:[8] Cost = (delivered concentration x fresh gas flow (4 L.min^{-1}) x time (min) x molecular weight (168) x cost of 1 mL) / [2412 x density desflurane (1.46)]. Cost analyses (in Euro) included costs for intra-operative drugs and drugs used in the PACU to treat pain and PONV. Costs for oxygen, staff (physician, nurses), disposables (cannulae, infusion lines, tubes, and so forth) and other overhead costs (such as anesthesia machines, monitoring) were not calculated. Prices for all drugs and resources were taken from our hospital pharmacy list; these were the prices that the patients pay. At the time of this writing, the exchange rate from the Turkish Lira (TL) to the EURO was 1 Euro = 1.750.000 TL (November 2005). Before the beginning of the study, a priori power

analysis revealed that a sample size of 20 patients per group would provide 80% power at $\alpha = 0.05$ to detect a difference in hemodynamic variable variations of 30%.

All statistical analyses were performed using SPSS for Windows version 12.0. The results are presented as mean ± standard deviation. Differences between the groups were tested using unpaired Student's t-test. Comparison of changes within the groups was analyzed using a repeated measures analysis of variance followed by post hoc Student-Newman-Keuls test. When criteria for parametric tests were violated, the appropriate non-parametric tests (namely Mann-Whitney U-test or Friedman's repeated measures analysis of variance on ranks) were applied. Descriptive variables were analyzed using the Chi-square test . A probability-value less than 0.05 was considered significant

Results. The patient characteristics are shown in **Table 1**. There were no statistically significant differences between the groups with regard to demographic variables, the duration of surgery and anesthesia. No statistically significant difference was found between the groups in MAP and HR values. Although not being substantially affected by skin incision, perioperative HR decreased significantly in both groups. **Figure 1a** shows the HR values of patients. One patient in Group TIVA had bradycardia (HR=49 beat.min^{-1}) which was treated with atropine. In both groups, MAP were significantly lower when compared to baseline values at 5, 15, 30 and 60 minutes intraoperatively ($p<0.05$). After this decrease, MAP remained stable until the time of extubation. However, the observed decreases in MAP were transient in both groups and easily controlled by IV fluid replacement and dose titration of remifentanil. **Figure 1b** shows the MAP values. The patient recovery profiles of the 2 groups are shown in **Table 2**. Recovery profiles between the 2 groups did not show any clinically significant difference. Visual analog scale scores were significantly higher in the first 5 and 10 minutes, in Group DES-REM than Group TIVA ($p<0.05$). Seven of 20 patients in Group DES-REM and 5 of 20 patients in Group TIVA, required meperidine 1 mg.kg^{-1} IM at PACU. The incidence of PONV was 15% in Group DES-REM and 5% in Group TIVA. Metoclopramide was administered to 3 patients in Group DES-REM, but none of the patients in Group TIVA. The cost analyses of patients are shown in **Table 3**. Anesthesia and postoperative care cost profiles between the groups did not show statistically significant difference. No significant differences were found in total costs at PACU as well.

Discussion. This study in patients undergoing septorhinoplasty demonstrated no differences between either desflurane-remifentanil or TIVA regarding hemodynamic effects, emergence from anesthesia and cost analyses. Anesthesia was smooth and uneventful with both anesthetic techniques. General anesthesia is the most frequently used anesthetic technique for septorhinoplasty operations. In this context, remifentanil is an alternative to N_2O as a useful analgesic agent. The use of large doses of this opioid blunts the hemodynamic responses to painful stimuli and greatly reduces the need for other co-anesthetics such as propofol or desflurane without prolonging recovery and postoperative respiratory depression.[9-11] We used the commonly acknowledged induction dose of 1 μg.kg^{-1} and infusion rate of 0.1 μg.kg^{-1}.min^{-1} for remifentanil infusion maintenance anesthesia.[9,12] Titration of remifentanil according to MAP and HR appeared to provide sufficient control in hemodynamic responses to intubation and surgical stimulation. Hemodynamics (HR and MAP) were mostly similar for both treatment groups. Similar results for remifentanil

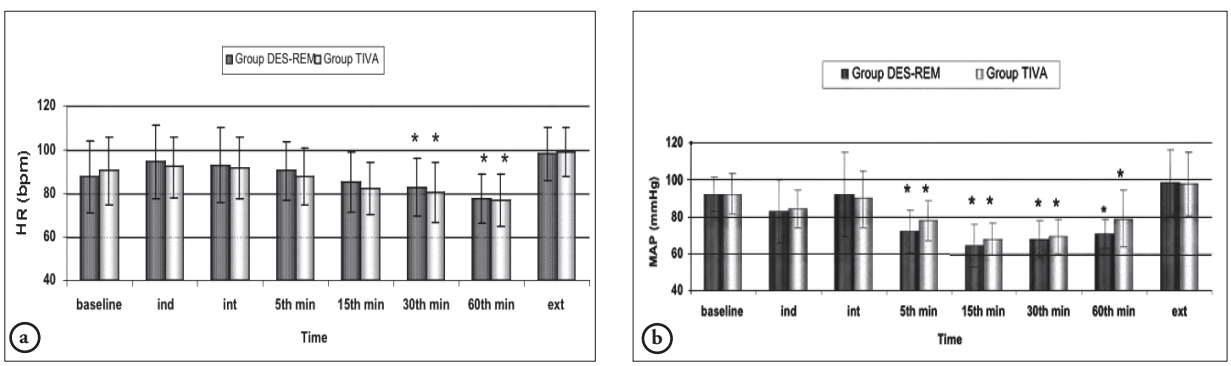

Figure 1 - **a)** Distribution of heart rate (HR) **b)** and mean arterial pressure (MAP) values. (ind=one minute after induction, int= one minute after intubation, ext= one minute after extubation) *$p<0.05$ compared to baseline values

Table 1 - Demographic data, duration of anesthesia and surgery in the both groups.

Demographic data	Group DES-REM (n=20)	Group TIVA (n=20)
Age (year)	26.4 ± 6	24.6 ± 6
Gender (F/M)	17/3	13/7
Weight (kg)	66.5 ± 8.4	68.2 ± 7. 7
Height (cm)	166.1 ± 8.8	168.2 ± 7.7
Duration of anesthesia (min)	83.4 ± 30.3	79.8 ± 20
Duration of operation (min)	69.8 ± 19.1	65.5 ± 15.2

Data are presented as mean ± SD, DES-REM -desflurane-remifentanil, TIVA - total intravenous anesthesia,

Table 2 - Recovery characteristics of groups.

Characteristics	Group DES-REM (n=20)	Group TIVA (n=20)
Extubation time (min)	7.3 ± 3.4	6.8 ± 3.7
Spontaneous eye opening (min)	7.8 ± 3.4	7.0± 3.9
Respond to verbal command (min)	8.7 ± 3.3	7.8 ± 3.7
Time to recover to the level of Aldrete recovery score >9 (min)	3.7 ± 1.7	2.8 ± 1.7
VAS 5th min	5.3 ± 2.9	3.5 ± 2,.2*
VAS 10th min	5.3 ± 2.7	3.7 ± 2.4*
VAS 15th min	4.9 ± 2.9	3.8 ± 2.3
Rescue analgesic (n)	7	5
PONV (n)	3	1
Rescue antiemetic (n)	3	-

Data are presented as mean ± SD, DES-REM -desflurane-remifentanil, TIVA - total intravenous anesthesia,
VAS - Visual analog scale; PONV- Post operative nausea and vomiting
*p<0.05 between the groups

Table 3 - Cost of anesthesia and postoperative care in the 2 groups.

Characteristics	Group DES-REM (n=20)	Group TIVA (n=20)
Induction	8.11 ± 0.87	7.83 ± 0.91
Maintenance	27.9 ± 9.81	24.35 ±10.59
PACU	0.19± 0.10	0.10 ± 0.13
Total cost	37.08 ± 9.84	34.25 ± 9.74

Dara are presented as mean ± SD, PACU- Postoperative Care Unit, DES-REM -desflurane-remifentanil, TIVA - total intravenous anesthesia, Prices were calculated by Euro at 2005

were reported by Chung et al.[13] They compared remifentanil in combination with isoflurane, enflurane or propofol undergoing short procedures and concluded that anesthesia combining remifentanil with volatile anesthetics or with propofol provided highly effective intraoperative analgesia and stable hemodynamics with rapid and almost identical emerging characteristics. In a systematic review focused on postoperative recovery and complications using different anesthetic techniques, the differences in early recovery times between propofol and desflurane were small and in favor of desflurane. However, no differences were found in home readiness or discharge between the anesthetics, in other study.[14] In a study of Grundmann et al,[15] which was conducted in laparoscopic cholecystectomies, similar recovery profiles were demonstrated in remifentanil-based anesthesia with propofol or desflurane. In agreement with this study, recovery profiles between the groups did not show clinically significant differences in the present study. The anti-emetic effect of propofol has been demonstrated in patients undergoing a variety of surgical procedures.[2,16,17] However, remifentanil has been demonstrated to increase the risk of PONV, probably by sensitizing the patient to movement after anesthesia, a mechanism similar for all opioid analgesics. Loop and Priebe[18] recorded that postoperative nausea and vomiting requiring treatment was less in group remifentanil-propofol compared to remifentanil-desflurane, remifentanil-sevoflurane, and alfentanil-isoflurane- N_2O. Although there was only one patient who experienced nausea after propofol, there were three patients who had transient nausea in the recovery area after desflurane anesthesia, in this study. However, we found no statistically significant difference in the frequency of PONV between the groups. Remifentanil is metabolized so rapidly that there is the possibility of a rapid decline in analgesia during emergence from anesthesia unless an analgesic infusion of remifentanil is maintained or a transition to another longer acting analgesic is made before emergence.[19] In a study of Ozkose et al[20] remifentanil-based TIVA was associated with earlier postoperative pain compared to alfentanil–based TIVA. Rosow[21] recommended additional longer lasting intraoperative opioids for postoperative analgesia when remifentanil was used for moderately painful procedure since the administration of additional long-lasting opioids intraoperatively might cause longer recovery and reduce the potential advantages of remifentanil. We did not continue remifentanil infusion at postoperatively, but meperidine 1 $mg.kg^{-1}$ IM was administered when VAS values were greater than 3 in both groups. Although there were 5 patients who received rescue analgesic in the TIVA group, there were 7 patients in the DES-REM group, but the difference was not statistically significant.

It is well known that intraoperative anesthesia costs are directly related to drugs and anesthetic techniques used.[22] The cost of inhalation anesthesia reduced in time by the use of low fresh gas flows.[23] The main waste with an inhaled anesthetic is that produced by unnecessarily high carrier gas flow. A clear advantage of desflurane protocol is the limiting of waste.[24] Rosenberg et al[24] recorded that in spite of cost similarity which has recently been implied between desflurane and propofol, their desflurane based general anesthetic technique was cost saving compared to their propofol general anesthetic technique. They have not compared desflurane to propofol per se, but rather one anesthetic technique to another.[24] We did not use low fresh gas flows and focused only on drug costs which are often only a small percentage of the overall costs of care. As the recovery profiles were similar, we assumed that staffing costs were equivalent for each group. Epple et al,[25] found that remifentanil and propofol was associated with lower intraoperative costs than the balanced anesthesia technique with isoflurane and fentanyl, in which all form, the actual acquisition costs of drugs, disposables and labor costs of physicians and nurses were calculated. Loop et al,[3] recorded that the waste of iv drugs increased overall anesthesia-related drug costs by approximately 20%, 30% and 50% in remifentanil-desflurane, remifentanil-sevoflurane and remifentanil-propofol. Remifentanil accounted for well over half of the anesthesia related drug costs, whereas propofol contributed one-third and desflurane and sevoflurane contributed only one fifth to the anesthesia-related drug costs. They confirmed the hypothesis that remifentanil-based anesthetic techniques were more expensive than a conventional technique using alfentanil, isoflurane and N_2O. They recorded that, although TIVA with remifentanil and propofol clearly tended to be more expensive than the combinations of remifentanil with desflurane or sevoflurane, this difference did not reach statistical significance. The results of our study are consistent with the findings of this study. Lack of such wastage when using inhalational anesthetics mostly explains why all remifentanil based techniques were more expensive than the conventional alfentanil-isoflurane-N_2O technique and why remifentanil-propofol technique tended to be the most expensive of all techniques. We found small difference in total costs, 37.08 ± 9.84 Euro for desflurane-remifentanil versus 34.25 ± 9.74 Euro for TIVA anesthesia which was not statistically significant. Reducing the percentage of wasted drugs, which was high in the remifentanil group, could decrease costs even more. Predictably, faster recovery in remifentanil groups may conceivably outweigh the higher drug costs by reducing physician and nursing labor costs, and by increasing operating room efficiency. In addition, lower incidence of PONV is likely to reduce medical staff costs in patients anesthetized with remifentanil-based techniques. Maintenance of gas pipelines and monitoring for environmental pollution associated with the use of N_2O and volatile anesthetics are relatively labor intensive and thus increase indirect costs of all anesthetic techniques based on volatile agents. If this was taken into consideration, TIVA techniques would become more cost effective. Although, Loop et al[3] did not directly calculate personnel costs, several of their findings suggest that medical staff costs might be lower in patients anesthetized with remifentanil. Because of predictably faster recovery, the average time interval between the end of surgery and transporting the patient out of the operating room was shorter in all remifentanil groups compared to alfentanil-isoflurane-N_2O.

In conclusion, both desflurane-remifentanil and propofol-remifentanil anesthesia provide perioperative hemodynamic stability, early and easy recovery with similar cost profiles for septorhinoplasty operations.

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