Effect of hypotensive anesthesia on cognitive functions

A comparison of esmolol and remifentanil during tympanoplasty

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ABSTRACT

Objective: To compare the effects of esmolol and remifentanil, used as adjuncts for induced hypotension on surgical conditions and short-term cognitive functions, during tympanoplasty.

Methods: The study was conducted in Hacettepe University, School of Medicine, Ankara, Turkey between January 2005 and December 2006 following Institutional Ethical Committee approval, 40 ASA I-II patients, between 18 and 60 years of age were included in this study. With the induction of anesthesia, for group E, an esmolol infusion of 50-250 $\mu g.kg^{-1}.min^{-1}$ was titrated, following a bolus of 0.5 $mg.kg^{-1}$; for group R, a remifentanil infusion of 0.2-0.5 $\mu g.kg^{-1}.min^{-1}$ was titrated; to achieve a mean blood pressure (BP) of 55-65 mm Hg. Arterial BP were recorded continuously throughout the operation. Mini Mental State Test (MMS) was performed at the preoperative 30th minute (MMS_p), postoperative 30th minute (MMS_{30}), 60th minute (MMS_{60}) and 24th hour (MMS_{24}). Surgical field was evaluated by the blinded surgeon, using a 6 point category scale.

Results: Patient demographics were similar in both groups. Sustained controlled hypotension was sufficient in all of the groups throughout surgery. Surgical field scores were lower in group R ($p<0.05$), although the scores were ≤2 in both groups, which was regarded as adequate for tympanoplasty. Four patients in group R (20%) and one patient in group E (5%) showed cognitive function decline between MMS_p and MMS_{30}. Within both groups, there were statistically significant differences between MMS_{60} and MMS_p, MMS_{24} and MMS_p, MMS_{60} and MMS_{30}, MMS_{24} and MMS_{30}, but the results were similar between the groups.

Conclusion: Remifentanil or esmolol provided adequate induced hypotension and similar operating conditions and their effects on cognitive functions in the short postoperative period are similar for tympanoplasty.

Saudi Med J 2007; Vol. 28 (9): 1357-1361

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Received 15th November 2006. Accepted 14th April 2007.

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Controlled hypotensive anesthesia is essential for maintaining a "dry" surgical field, during operations performed under microscope, like tympanoplasty, which will provide a better surgical field visualization and result in ease in operation technique and shortened duration of surgery. During general anesthesia, providing effective hemodynamic control with minimal mental and cognitive side effects, by using short-acting and safe adjuncts is important for ambulatory surgery or operations that need very short hospitalization. Previous reports show that hypotension with a mean arterial pressure (MAP) between 50-60 mm Hg affects cognition.[1] Various drugs have been used to facilitate the induction of controlled hypotension for middle ear surgery, including vasodilators such as sodium nitroprusside, nicardipine, nitroglycerine, inhaled anesthetics, remifentanil and esmolol.[2-4] Esmolol hydrochloride is an ultra short-acting (t1/2: 9 minutes), intravenous, cardioselective ß1-adrenergic receptor blocker, easily titratable to the desired ß-adrenergic blockade level and rapidly discontinued when clinically indicated.[5] Remifentanil is a potent µ-opioid agonist, with a very short onset of action. It shows rapid recovery, due to rapid degradation by non-specific blood and tissue esterases.[6] After prolonged infusions, it does not show accumulation and can easily be titrated intraoperatively, without resulting in a prolonged postoperative recovery. Previous reports show that both remifentanil and esmolol could be safely used during anesthesia for tympanoplasty or other types of surgeries, for providing hemodynamic stability and a rapid emergence from anesthesia, with few side effects.[2,7] The

efficacy of esmolol and remifentanil with combination of desflurane have not been compared previously in ear surgery according to bleeding, quality of the operative field and cognitive functions with a MAP between 55-65 mmHg. We hypothesized that these agents may have different effects on cognitive function during induced hypotension, due to different mechanisms of hypotension. Accordingly, this prospective study was designed to compare the effects of remifentanil and esmolol combined with desflurane on the quality of surgical conditions and short-term cognitive functions, during tympanoplasty.

Methods. The study was performed in Hacettepe University, School of Medicine, Department of Anesthesiology, and Reanimation in 2006. We have conducted this prospective, randomized study in ASA I-II patients, between ages of 18 and 50, undergoing tympanoplasty. Patients with hypertension, arrhythmias , congestive heart failure, coronary arterial disease, history of myocardial ischemia and cerebrovascular attack, neuropsychiatric disorders and known allergic reactions of any kind to the study drugs were excluded from the study. Detailed medical history and demographic information of the patients were obtained, as well as their history of alcohol and drug consumption. A minimum education of 11 years was required from the patients. We included patients aged 18-50 years with no accompanying systemic disease who underwent tympanoplasty for various indications. The study was approved by University Ethical Committee and written informed consent was obtained from all participating patients. Fasting of 8 hours was required, and the patients did not receive any premedication. Intraoperative monitors consisted of continuous electrocardiography (ECG) and pulse oximetry, and invasive arterial blood pressure monitorization, through a 20-gauge catheter, inserted into the radial artery. Ringer's solution, with a rate of 5-10 $ml.kg^{-1}.hr^{-1}$ was started through an 18-gauge intravenous catheter. Anesthesia was induced with intravenous propofol 2.5 $mg.kg^{-1}$, fentanyl 1.0 $\mu g.kg^{-1}$, and vecuronium 0.1 $mg.kg^{-1}$. For maintenance, desflurane 7% and air 50% in oxygen were used. Patients were mechanically ventilated, adjusted to provide an end-tidal CO_2 pressure of 30-35 mmHg. No additional anesthetic or analgesic drug was administered, and desflurane concentration remained stable throughout the operation. Vital signs of the patient were recorded every 5 minutes, along with the study parameters. Any intraoperative complication (excessive hypotension, hypertension, tachycardia, bradycardia, agitation, vomiting during recovery from anesthesia), along with operational and anesthesia times were recorded.

The patients were allocated into 2 groups according to a computed randomization list: Group E (esmolol) and group R (Remifentanil). Group E consisted of 20 patients. With the anesthesia induction, prior to endotracheal intubation, a bolus of 0.5 $mg.kg^{-1}$ intravenous esmolol was administered in 30 seconds and an esmolol infusion of 50-250 $\mu g.kg^{-1}.min^{-1}$ was initiated.[8] Group R consisted of 20 patients. With the anesthesia induction, a remifentanil infusion of 0.2-0.5 $\mu g.kg^{-1}.min^{-1}$ was initiated. Esmolol and remifentanil infusion rates were titrated to maintain the MAP between 55-65 mmHg throughout the operation. With the withdrawal of the microscope away from the surgical area, infusion doses of esmolol and remifentanil were decreased by 50% and they were stopped at the end of surgery. Neuromuscular blockade was antagonized with neostigmine and atropine. With eye opening and response to a verbal command, the patients were transferred to the recovery room. The surgical conditions for a bloodless operative field were rated every 10 minutes by the same attending surgeon, who was blinded to the pharmacological agent used and the patient groups. The category scale for intra-operative surgical field evaluation[3] was used (**Table 1**). The medians of the surgical field scores obtained throughout the operation were calculated for each patient, and they were compared among groups. Ideal category scale values for optimal surgical conditions were defined as ≤2. No local vasoconstrictor was used throughout the surgery to provide control of bleeding.

Mini Mental State Test (MMS)[9] was used for evaluation of cognitive functions. The MMS was chosen because it is easily applicable, highly valid, and reliable, enabling frequent application. It consists of 11 questions, evaluating orientation to time and places, registration, attention, calculation, short-term recall, language ability, and constructional ability. The MMS was performed 30 minutes before entry of the patient to the operating room (MMS_p), 30 (MMS_{30}) and 60 (MMS_{60}) minutes after extubation of the patient, at the recovery room, and at the postoperative 24th hour (MMS_{24}), by the same anesthesiologist, trained in the use of the test and blinded to the patient group allocation. The maximum score being 30 points, a difference of 2 or more was recorded as cognitive function decline and a score lower than 23 was recorded as cognitive impairment. Before MMS_{30} and MMS_{60} evaluations, Aldrete post-anesthesia recovery score[10] was obtained for each patient at the post operative 30th and 60th minutes, so that cognitive function testing would only be applied to patients with the similar post-anesthesia recovery state. An Aldrete Score ≥7 was considered as the patient being awake and MMS was applied. The anesthesiologist, performing the MMS and Aldrete Score evaluation was blinded to the drug group of

patients but the anesthesiologist intraoperatively giving the anesthesia was not. At the recovery room, following the completion of MMS_{60} and the patient's meeting our discharge criteria (the patient being alert and oriented, talkative and cooperative, with adequate pain control, minimal nausea, or vomiting and stable vital signs), they were transferred to the ward. All adverse reactions (nausea/vomiting, agitation, hemodynamic instability, excessive post-operative pain, need of extra medication) and complications during the operation and at the recovery room were recorded.

Statistical analysis of the data was carried out using SPSS (Statistical Package for Social Sciences) 12.0 for Windows. T-test was used for assessment of mean surgical field values and operational time (p<0.05 was statistically significant); Chi-Square tests for intraoperative and postoperative complications (a p value <0.05 was statistically significant), MMS evaluations were made with Chi-Square tests (p<0.05 was statistically significant) and Wilcoxon Signed Ranks Test (p<0.08 was statistically significant). A sample size of 20 was determined by using a power analysis based on the assumptions that a) the incidence of postoperative cognitive impairment at one hour after anesthesia would be 50% b) a 70% reduction (from 50-15%) would be of clinical significance, and c)"a= 0.05, b=0.2.

Results. The 40 ASA I-II patients, 17 male and 23 female, aged between 18 and 58 were in this study. Two groups were similar, according to patient demographics (**Table 2**). Anesthesia and surgery times were also similar in both groups (**Table 3**). The MAP values, previously projected for sufficient hypotension were achieved in both drug groups, the MAP mean values being 55 ± 3.2 mmHg for group R and 60 ± 4.3 mmHg for group E. The MAP values were similar in both groups. Medians of surgical field evaluation scores were 2 (0-3, 5-95%) for group E and 1.75 (0-2, 5-95%) for group R (**Table 3**). This was statistically significant (2-Tailed Test, p=0.004).

Aldrete Scores of all patients, at the post operative 30th and 60th minutes, in both groups were ≥7. All the patients were regarded as awake during MMS testing. The MMS scores of the patients in Group E are shown in **Table 4**. The differences between MMS_{60} and MMS_p (p = 0.002), MMS_{24} and MMS_p (p = 0.001), MMS_{60} and MMS_{30} (p = 0.004), MMS_{24} and MMS_{30} (p = 0.003) were statistically different (Wilcoxon Signed Ranks Test). The MMS score drop between MMS_{30} and MMS_p and the increase of scores between MMS_{60} and MMS_{24} was not statistically significant (**Table 4**). The MMS scores of the patients in group R are shown in **Table 4**. The differences between MMS_{60} and MMS_p (p=0.005), MMS_{24} and MMS_p (p=0.001), MMS_{60} and

Table 1 - Category scale for intraoperative surgical field evaluation.

Score	Definition
0	No bleeding
1	Mild bleeding - No need of blood aspiration
2	Mild bleeding - Occasional aspiration necessary. Clear surgical field.
3	Moderate bleeding - Frequent aspiration necessary. Bleeding closes surgical field a few seconds following aspiration.
4	Moderate bleeding - Frequent aspiration necessary. Bleeding closes surgical field right after aspiration.
5	Excessive bleeding - Continuous aspiration necessary. Bleeding appears faster than aspiration. Surgical field is closed and surgery is not possible.

Table 2 - Patient demographics.

Parameter	Group E n=20	Group R n=20
Male to female ratio (n)	9:11	8:12
Age (years) (mean±SD)	32.55 ± 10.96	37.65 ± 12.5
Weight (kg) (mean±SD)	72.10 ± 11.36	67.40 ± 10.20
Education n (%)		
High school graduate	15 (75)	12 (60)
University graduate	5 (25)	8 (40)

Table 3 - Intraoperative parameters.

Parameters	Group E mean±SD	Group R mean±SD	*P*-values
Anesthesia time (min)	120.2 ± 38.74	110.3 ± 34.47	0.325
Surgery time (min)	99.5 ± 38.00	89 ± 34.47	0.236
p=0.041, Likelihood Ratio			

Table 4 - Mini Mental State Test (MMS) scores and evaluation results.

Tests	Group E mean±SD	Group R mean±SD
MMS_p	28.75 ± 1.44	28.70 ± 1.49
MMS_{30}	28.60 ± 1.69)	28.10 ± 2.59)
MMS_{60}	29.65 ± 0.87	29.35 ± 1.26)
MMS_{24}	29.90 ± 0.44	29.75 ± 0.63
Cognitive function decline (%)	2 (10)	4 (20)
Cognitive impairment (%)	0	1 (5)

MMS_{30} (p = 0.006), MMS_{24} and MMS_{30} (p = 0.003) were statistically different (Wilcoxon Signed Ranks Test). The MMS score drop between MMS_{30} and MMS_{p} and the increase of scores between MMS_{60} and MMS_{24} was not statistically significant.

In group E, a decline in cognitive functions was seen in 2 patients (10%); while in group R, 4 patients (20%) showed cognitive function decline. This was not statistically significant between groups. In group E, no patient showed cognitive function impairment. In group R, one patient showed impairment, with an MMS score of 20, measured at the postoperative 30th minute. Again, there was no statistically significant difference between 2 groups.

Intraoperatively, the only experienced complication was bradycardia (heart rate <40 beats/min), seen in 3 patients in group E (15%) and 4 patients in group R (20%). The patients responded well to atropine 0.5 mg. At the recovery room, 4 patients from each group experienced nausea/vomiting and required antiemetics. The ECG evaluations for ischemia showed no significant difference during the hypotensive periods, for both groups. There were no postoperative respiratory and circulatory complications in either group. Postoperative analgesic requirements were not different between 2 groups.

Discussion. After surgery, patients may suffer a decline in cognitive function. The etiology of postoperative cognitive dysfunction (POCD) is likely to be multifactorial. General anesthesia, anesthetic agents or the postoperative analgesic regiment can cause POCD. Other factors such as the inflammatory or metabolic endocrine stress responses associated with major surgery and hypotension may also be important. Increased age, increased duration of anesthesia, less education, a second operation, postoperative infections, and respiratory complications have been identified as risk factors for early postoperative cognitive dysfunction.[11] On the contrary, only age was a factor for late postoperative cognitive dysfunction and neither hypoxemia nor hypotension was found to affect cognitive functions at any time.[11]

Many techniques have been set up to deal with bleeding in middle ear surgery, but none of them are ideal. Remifentanil was effective in reaching ideal MAP values and ensured good surgical conditions in our study and just as other recent studies.[2,4] In our study, esmolol demonstrated similar hemodynamic effects and good surgical conditions during tympanoplasty. It has been reported that for tympanoplasty, a bloodless surgical field would occur with a MAP of 50 ± 5.1 mmHg.[8] Our intraoperative target MAP was 55-65 mmHg for a clear surgical field. We had predicted that surgical field scores ≤2 would be our projected values for a bloodless surgical field and medians of surgical field scores were 2 (0–3, 5-95%) for group E and 1.75 (0-2, 5-95%) for group R. Although this difference was statistically significant, both groups achieved our target surgical field values for satisfactory surgical exposure. In our study, cognitive function impairments, observed in MMS_{30} scores can be attributed to the residual effects of general anesthesia and surgical stress, despite controlled hypotension, or the hypotensive anesthesia technique, as both agents are accepted to have their effects for only very short periods of time, once they are stopped and both agents have no residual effect. We have attributed the relatively lower scores of MMS_{p}, when compared with MMS_{60} and MMS_{24} to preoperational anxiety, fasting of 8 hours and not being familiar with the MMS testing. At the postoperative period, once the patients were relieved from their preoperational anxiety, and got accustomed to MMS testing, they were more relaxed and eager to complete the test. Also, in accordance with the MMS_{24} results, obviously MMS testing has a learning effect, which resulted in higher MMS scores. Remifentanil has been shown to decrease anesthetic agent requirement, which resulted in faster recovery of the patient, along with the cognitive functions.[12,13] Also, when used as the sole anesthetic, it provided shorter emergence times and faster recovery of the cognitive functions, when compared with propofol.[14] Effective β-blockade with esmolol was also shown to bear no effects on cerebral blood flow, cerebrovascular reactivity, or cognitive performance on healthy volunteers.[15] Also, the adjunctive use of esmolol during desflurane-based anesthesia has been shown to provide a more rapid awakening from anesthesia, reduce the postoperative opioid analgesic requirement and decrease the time to discharge home after ambulatory laparoscopic surgery.[16] Different intervals have been used to evaluate postoperative cognitive functions, with different anesthetic approaches. Chung et al,[9] in their study of patients older than 60 years of age, showed that there was a significant decrease in mental functions at the postoperative 6th hour, independent of the anesthetic approach, general anesthesia, or spinal anesthesia with sedation. In their study of elderly patients, undergoing desflurane or sevoflurane anesthesia, Chen et al[17] have stated that at the postoperative 60 minutes, 51% of patients in desflurane group and 57% of patients in sevoflurane group showed significant decreases in cognitive function. In 3 hours, 85% of the patients returned to their basal cognitive function levels and at the postoperative 24-hours, all patients but one had normal basal MMS scores. Our cognitive impairment findings for groups E (10%) and R (20%), are far more different than findings in these studies. However, our study population was much younger compared from

the previous study. These findings coincide with the results of Moller et al.[11]

Many years ago, it was speculated that POCD may occur as a result of physiological changes during anesthesia and surgery, which adversely affects cerebral perfusion.[18] Unfortunately, the results and the mechanisms are not definite. Accordingly, we hypothesized that these agents could have different effects on cognitive functions. But, our study showed that, in our young population of patients with a MAP of 55-65 mm Hg, these agents did not show any superiority to each other on short term cognitive functions. This may be caused by the young population of patients, short surgical time and lack of bleeding. Another reason may also be that, there may not be a difference between 2 drugs regarding the mechanism of action on cognitive functions. To understand this better, these 2 drugs may be compared in an older population of patients with particular risks that may detoriate cognitive functions.

In conclusion, the present study has showed that both esmolol and remifentanil provided adequately controlled hypotension, with similar effects on short term postoperative cognitive functions and they can safely be used during tympanoplasty.

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