ORIGINAL ARTICLE

Comparison of remifentanil with esmolol to blunt the cardiovascular response to tracheal extubation in patients undergoing neurosurgical procedures for intracranial masses

Hamzeh Hosseinzadeh,[1] Mahmood Eidi,[2] Mehdi Ghaffarlou,[3] Effat Torabi,[4] Kamyar Ghabili,[5] Samad Eslam Jamal Golzari[6]

Abstract

Objective: To compare the efficacy of esmolol with remifentanil in maintaining haemodynamic stability at the end of a neurosurgical procedure and recovery stages and reducing the length of the recovery phase.

Methods: The double-blind prospective randomised clinical trial was conducted at Imam Reza Hospital, Tabriz, Iran, from May 2010 to November 2011. It comprised 90 adult patients who were scheduled to undergo elective neurosurgery operations and were randomly divided into three groups receiving esmolol, remifentanil and placebo for 14 minutes. The intravenous infusion was started four minutes prior to extubation and continued for 10 minutes after extubation. SPSS 16 was used for statistical analysis.

Results: There was a significant difference between the three groups regarding the changes of mean arterial pressure after extubation and five minutes after extubation ($p<0.001$ in all groups). The esmolol group compared with the placebo group and the remifentanil group compared with control group were of significant difference at all heart rate values after extubation ($p<0.001$ in all cases). A significant difference regarding SaO2 levels was observed between the remifentanil and esmolol groups 5 ($p<0.01$), 10 ($p<0.01$) and 15 minutes after extubation ($p<0.005$).

Conclusion: Both esmolol and remifentanil can be used in preventing hyperdynamic status throughout the extubation phase without extending the recovery phase. However, due to more frequent respiratory suppression and prolonged extubation observed in the remifentanil group, its administration should be done with caution.

Keywords: Remifentanil, Esmolol, Neurosurgery, Cardiovascular stability. (JPMA 63: 950; 2013)

Introduction

Emergence from general anaesthesia and especially post-extubation phase are the stages associated with cardiovascular hyperdynamic status leading to increase in oxygen consumption, and catecholamine release. This phase lasting 15 to 5 minutes could frequently be accompanied by tachycardia and hypertension.[1] Most patients, however, endure this temporary situation appropriately.[2] On the other hand, patients having pre-operative hypertension and cardiovascular and cerebrovascular diseases and patients with increased intracranial pressure (ICP) could be affected by severe cardiac and or cerebral complications.[3] Therefore, it is of great importance to prevent post-operative and post-intubation sympathetic excitations in high-risk patients as maintaining stability in the dynamic status reduces mortality and morbidity rates in these patients.[1] Esmolol, a selective beta-adrenergic receptor antagonist, is water-soluble, short-acting (9 minutes) and of a rapid effect commencement. Administering esmolol through an anaesthesia session reduces hyperdynamic cardiovascular responses. Remifentanil hydrochloride is a recent μ agonist receptor which is being associated with better haemodynamic stability under surgical stress conditions compared with other narcotics such as fentanyl,[4,5] or alfentanyl.[6] Remifentanil could be associated with low to moderate hypotension.[7] Considering the fact that pain is one of the major factors contributing to sympathetic excitement at the end of the surgery and recovery stages, the current study aimed at evaluating the efficacy of pre-extubation administration of esmolol and remifentanil in maintaining haemodynamic stability at the end of the surgery and recovery stages, and their effects on the length of the recovery phase.

Patients and Methods

The double-blind prospective placebo-control randomised clinical trial was carried out at the Imam Reza Hospital, Tabriz, Iran between May 2010 and November 2011. After obtaining approval of the Ethics Committee of the faculty of medicine, Tabriz University of Medical Sciences, and informed written consent from the subjects, 90 adult patients with American Society of Anaesthesiologist (ASA) Class I-II who were scheduled to undergo elective neurosurgery operations for their intracranial masses, were included. Sample size was

[1-4]Department of Anesthesiology, [5]Tuberculosis and Lung Disease Research Centre, [6]Medical Philosophy and History Research Centre, Students' Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.

Correspondence: Samad Eslam Jamal Golzari. Email: dr.golzari@hotmail.com

calculated using an online calculator. Randomisation was also achieved through a web-based software. Patients were randomly divided into three equal groups of 30 each. Pregnant females, patients with heart rate less than 60, systolic blood pressure (SBP) less than 100-mmHg, considerable hepatic, renal or cardiovascular complications, atrioventricular block, sick sinus syndrome, history of intolerance to beta-blockers, bronchospasm and asthma, and chronic obstructive pulmonary disease (COPD) were excluded. Data was collected on a pre-designed proforma by someone who was blinded to the study. All patients were pre-medicated with fentanyl (2µg/kg, IV) and lidocaine (1.5mg/kg, IV), and intubated using sodium thiopental (7-5mg/kg) and cisatracurium (0.15mg/kg). Anaesthesia was maintained using isoflurane (1-1.5%) and a mixture of oxygen (O_2) (50%) and nitrous oxide (N_2O) (50%). Mechanical ventilation was maintained with a tidal volume of 10 mL/kg and at a rate to keep End-tidal carbondioxide (CO_2) at the range of 35-30mmHg. Repeated doses of cisatracurium (0.05mg/kg) were used to provide intraoperative muscle relaxation. Administration of anaesthetics was terminated when suturing the skin, and muscle relaxation was antagonised with neostigmine (0.05mg/kg) and atropine (0.02mg/kg) after the re-establishment of spontaneous breathing.

In group 1, intravenous (IV) infusion of esmolol (0.5mg/kg) was administered within 4 minutes prior to the extubation which continued by an IV infusion of esmolol at the rate of 0.15mg/kg/min for 10 minutes after extubation. In group 2, IV infusion of remifentanil (0.2µg/kg) was administered within 4 minutes prior to the extubation which continued by an IV infusion of remifentanil at the rate of 0.1µg/kg/min for 10 minutes after extubation. In control group, IV infusion of normal saline (0.5ml/kg) was administered within four minutes prior to extubation which continued by an IV infusion of normal saline at the rate of 0.15ml/kg/min for 10 minutes after extubation.

Medications were prepared and coded previously by a colleague so that the co-worker keeping the records was unaware of the contents of the syringes. All patients were given IV lidocaine (1.5mg/kg) 90 seconds prior to the extubation. Systolic and diastolic blood pressure, mean arterial pressure and heart rate were recorded before and after medication administration and extubation. Vital signs were recorded every 5 minutes in the recovery phase until the patient was discharged from the recovery unit. The same monitors were used for all patients (Lohmeier 11, Germany). Time required for performing eye-opening to verbal commands, spontaneous eye opening and a recognition of the location and people at the recovery unit were recorded for all groups.

To achieve a power of 80% with a type I error rate of 0.05, the sample size was calculated as 30 patients for each group. Data was analysed using SPSS16. To evaluate the statistics, descriptive statistical approaches (frequency, percentage, mean and standard deviation) were used. To compare qualitative variables, chi-square test, and to compare quantitative variables, independent t-test was used. The changes in quantitative findings throughout the study in groups were evaluated using repeated measure of analysis of variance (NOVA). A p less than 0.05 was considered statistically significant.

Results

Basic demographic characteristics of patients in the 3 groups were noted and no statistically significant difference was found ($p>0.05$; Table-1). The aetiologies requiring surgeries included 15 (16.7%) cases of frontal tumours, 14 (15.6%) cases of cerebral tumours, 12 (13.3%) cases of pituitary gland adenoma, 8 (8.9% each) cases of posterior fossa tumours and meningioma, 4 (4.4% each) cases of cerebral aneurysms, temporal tumours and occipital tumours, 3 (3.3% each) cases of suprasellar tumours and cerebral hydatid cysts, and 15 (16.7%) cases with other lesions. All the 90 patients met the extubation criteria at the end of the surgery and were successfully extubated on the operating table. None of the patients required post-operative ventilation. The changes in the levels of SBP revealed no significant difference in any group at all values before extubation ($p<0.07$). Furthermore, the esmolol group was associated with significantly lower levels of SBP compared with the

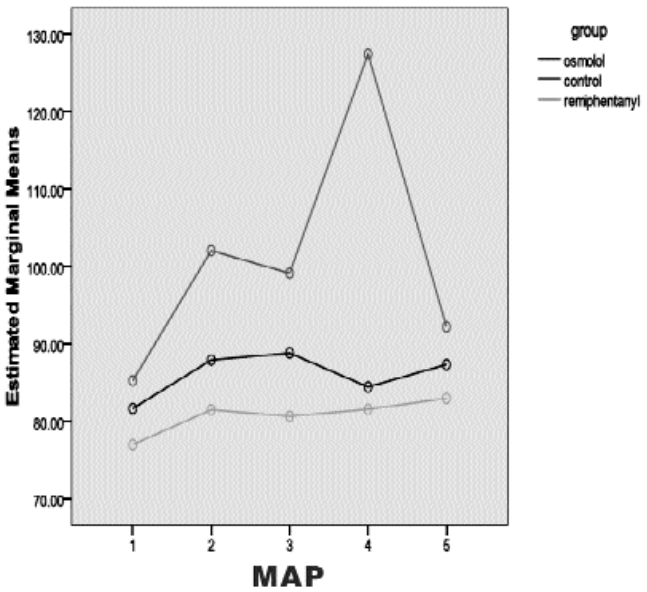

Figure-1: Changes in mean arterial pressure (MAP) in the three groups.

Control group after extubation (p<0.001), 5 (p<0.001), 10 (p<0.001), and 15 minutes (p<0.001) after extubation. Despite the lower levels of SBP at different stages in remifentanil group compared with the esmolol group, the difference was not statistically significant (p>0.05).

The study of the changes in diastolic blood pressure (DBP) in all groups revealed a significant higher levels in the control group compared with the other groups, and also higher levels in the esmolol group compared with the remifentanyl group at most stages (Table-1).

In terms of mean arterial pressure (MAP) in the three groups, there was a significant difference after extubation and 5 minutes after extubation (p<0.001 in all groups). The remifentanil group was significantly associated with lower mean MAP levels compared with the control group before extubation (p<0.01), after extubation (p<0.001), 5 minutes (p<0.001) and 15 minutes (p<0.01) after extubation. The esmolol group was only associated with significant difference regarding lower MAP 5 minutes after extubation (p<0.01), (Figure-1).

A significant difference was observed in heart rate in all three groups at all values (p<0.001 in all cases). Furthermore, the esmolol group, compared with the control group and remifentanil group compared with the control group were of significantly lower heart rate values after extubation (p<0.001 in all cases); significantly lower heart rate values were observed in the remifentanil group compared with the control before extubation (p< 0.04), (Figure-2). However, the difference between remifentanil and esmolol groups was not significant at any of the measured values. Repeated measure of ANOVA revealed a significant difference regarding heart rate in three groups (p<0.001). Dysrhythmia was not reported in any of the groups.

The levels of arterial oxygen saturation (SaO_2) at different stages in the three groups were significantly different (Table-2). The difference between remifentanil and control groups after extubation (p<0.03) and 5 minutes after extubation was significant, with higher levels in the

Table-1: Demographic findings and changes in oxygen saturation levels (%) and systolic and diastolic blood pressure values in the three groups.

	Control group	Esmolol group	Remifentanil group	P-value
Age (year)	49.03±17.00	46.00±16.25	43.62±15.83	0.49
Gender (M/F)	9/21	15/15	16/14	0.14
Weight (kg)	71.57±12.02	73.17±10.33	66.82±11.08	0.08
Operation duration (minutes)	186.56±62.65	184.65±42.71	193.27±38.80	0.78
ASA (II/I)	16/14	15/15	11/19	0.39
O2 saturation before extubation (%)	98.00±2.42	97.83±2.33	98.93±1.46	0.1
O2 saturation immediately after extubation (%)	96.70±2.69	97.30±2.24	98.13±2.31	0.07
O2 saturation 5 mins after extubation (%)	96.36±2.98	97.43±1.92	98.53±1.54	0.001
O2 saturation 10 mins after extubation (%)	97.55±2.39	97.53±1.52	98.53±1.54	0.06
O2 saturation 15 mins after extubation (%)	97.56±2.12	97.55±1.54	98.63±1.27	0.03
Systolic blood pressure before extubation (mmHg)	14.93±115.63	17.61±109.7	15.83±104.86	0.07
Systolic blood pressure immediately after extubation (mmHg)	21.1 ±137.86	17.2± 115.9	15.12 ±109.8	0.04
Systolic blood pressure 5 mins after extubation (mmHg)	21.94 ± 134.36	16.16±116.3	18.99±110.53	<0.001
Systolic blood pressure 10 mins after extubation (mmHg)	24.09±132.43	17.6±112	17.2±109.93	<0.001
Systolic blood pressure 15 mins after extubation (mmHg)	17.21±125.81	17.19±113.96	14.3±110.5	0.002
Diastolic blood pressure before extubation (mmHg)	13.09±71.9	13.46±69.73	16.26±80.93	0.68
Diastolic blood pressure immediately after extubation (mmHg)	15.85±85.13	14.3±79.26	13.65±67.7	<0.001
Diastolic blood pressure 5 mins after extubation (mmHg)	18.92±85.56	13.93±77.43	13.92±68.23	<0.001
Diastolic blood pressure 10 mins after extubation (mmHg)	23.64±84.33	14.02±72.16	13.94±68.7	0.003
Diastolic blood pressure 15 mins after extubation (mmHg)	12.68±76.59	13.96±74.62	13.48±69.66	0.13

ASA: American Society of Anaesthesiologists. O2: Oxygen.

Table-2: The mean of extubation and recovery phase length in the three groups (minutes).

	Control group	Esmolol group	Remifentanil group	P-value
Extubation	4.58±1.76	4.43±1.59	7.86±2.82	<0.001
Eye-opening with verbal commands	12.48±3.37	11.66±3.85	12.80±3.12	0.43
Spontaneous eye-opening	16.17±4.53	15.80±4.83	16.56±3.48	0.79
Orientation	21.03±6.17	20.43±6.55	21.36±4.99	0.82

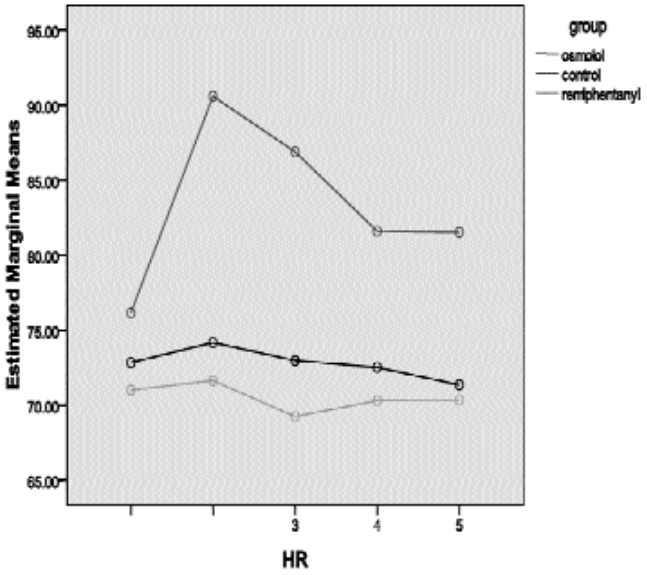

Figure-2: Changes in heart rate (HR) in the three groups.

remifentanil group (p<0.001). Besides, a significant difference regarding SaO_2 levels was observed between remifentanil and esmolol groups 5 minutes (p<0.01), 10 minutes (p<0.01) and 15 minutes (p<0.005) after extubation with higher levels in the remifentanil group. No significant difference was observed between esmolol and control groups in this regard. Repeated measure of ANOVA revealed a significant difference regarding the changes in SaO_2 levels among the three groups (p<0.008).

A significant difference was observed regarding extubation phase length in the three groups, remifentanil and esmolol groups (p<0.001), and remifentanil and control groups, with longer phases in the remifentanil group (p<0.001).

Discussion

Patients with hypertension and cardiovascular or cerebrovascular diseases and patients with increased ICP could accompany severe cardiac or cerebral complications at extubation phase.[3,10] Therefore, managing haemodynamic responses, such as heart rate and blood pressure, while disconnecting from mechanical ventilation would be of great importance. Numerous strategies have been introduced to prevent haemodynamic responses caused by emergence from anaesthesia, including extubation under deep anaesthesia, administration of local anaesthetics, vasodilators and short-acting opioids.[11] Administering vasodilators, such as sodium nitroprusside, nitroglycerine and hydralasine, could be associated with complications like reflexive tachycardia and increase in the plasma rennin activity.[2]

One of the most frequently used medication groups is opioids. In modern anaesthesia, mostly to prevent a hyperdynamic cardiovascular status followed by tracheal intubation, fentanyl is used. In a study,[10] fentanyl was introduced to prevent hyperdynamic cardiovascular status followed by extubation. The current study selected remifentanil because of its short-acting characteristic which would not prolong the recovery phase. Different studies have concluded that remifentanil, compared with other opioids including fentanyl and alfentanil, is accompanied with a more stable haemodynamic status under surgical stress.[8,10,13]

Beta-adrenergic blockers are also frequently used to suppress adrenergic activity caused by extubation, especially throughout neurosurgery operations.[14,15] In the present study, esmolol, a selective short-acting beta-blocker, was administered and its preventive characteristics against cardiovascular responses caused by extubation in the surgeries involving cerebral masses were compared with that of remifentanil. The results revealed that both esmolol and remifentanil could be administered to prevent haemodynamic instability caused by extubation. It has previously been proven that hyperdynamic cardiovascular status caused by sympathetic excitation followed by extubation could be endured for 5 to 10 minutes.[1] Considering the fact that esmolol and remifentanil are of very short half-life, in addition to administration of a bolus does before extubation, we used IV infusion of these medications within 10 minutes after extubation which was associated with desirable results.

In a similar study,[16] haemodynamic changes were reported to be more frequent in the control group compared with the remifentanil group. In one study,[2] it was stated that esmolol had the characteristic of preventing hyperdynamic status. In another study,[17] haemodynamic changes were also less in the esmolol group compared with the control group. One study reported that esmolol, especially in higher doses, can reduce blood pressure (BP) and (HR) increase followed by extubation.[18] In the present study, the remifentanil group had a longer extubation time compared with the other two groups which could be explained by the dose-dependent respiratory suppression effect of opioids.[19] However, one study[16] observed no significant difference between the remifentanil and control groups regarding the length of extubation time which could have been due to genetic differences.

An appropriate anaesthetic for neurosurgery should provide the possibility of early evaluation of the neurologic status of the patients and early diagnosis of potential post-operative complications (for instance; haematoma and major cerebral oedema) by a rapid and short recovery phase.[20] In the present study, there was no significant

difference among the three groups regarding the time of eye-opening (to verbal commands and spontaneous) and the recovery phase length. In a study,[20] the most significant difference between remifentanil and controls was observed regarding the time of eye-opening and discharge from the recovery unit. Others also reported no significant change in the recovery phase length followed by administration of a bolus dose of remifentanil.[21] However, in one study,[2] the time of eye-opening (to verbal commands and spontaneous) was recorded to be shorter in the esmolol group compared with the control group.

Sympathetic excitation followed by extubation would lead to increase in MAP and HR and, therefore, the patients at risk of cardiovascular and cerebral complications should be prevented from these excitations. Both esmolol and remifentanil could be used in preventing hyperdynamic status throughout the extubation phase without extending the recovery phase length. However due to more frequent respiratory suppression and prolonged extubation observed in the remifentanil group, the administration of this medication should be performed cautiously.

The current study had a limitation, as while calculating the sample size, due to lack of adequate previous articles on the subject, the effect size was not used.

Conclusion

Esmolol may be administered as the medication of choice, while remifentanil may be used in cases in which more aggressive control of the haemodynamic status is required in high-risk patients undergoing intracranial surgeries. A combination of both medications with more balanced doses would probably be associated with more favourable results.

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