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The Efficacy of Esmolol to Blunt the Haemodynamic Response to Endotracheal Extubation in Lumbar Disc Surgery

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Abstract: In this study, we aimed to determine the efficacy of esmolol infusion to prevent the hyperdynamic state which occurs during the recovery period and after extubation in the patients having lumbar disc surgery under general anesthesia. Forty five patients who would undergo elective lumbar disc surgery were randomly divided into three groups and general anesthesia was induced with 5-7 mg kg^{-1} sodiumthiopental and 0.5 mg kg^{-1} atracurium; it was maintained with isoflurane in 50/50 % oxygen-air mixture and 0.1-0.3 μg $kg^{-1}min^{-1}$ remifentanil infusion. On the completion of the surgery both of the goups (Group E1 and GroupE2) received esmolol 0.5 mg kg^{-1} as a loading dose. Following the 4 min infusion, Group E1 patients were administered 0.1 mg kg^{-1} min^{-1} esmolol while GroupE2 patients received 0.2 mg kg^{-1} min^{-1} esmolol infusion and it continued till 10 min after extubation. The control group (Group C) patients received the same dose of saline infusion for the same duration. Heart rate was significantly higher in control group than those in groups E1 and E2 at 5th and 10th min of esmolol infusion. Also mean arterial pressure was higher in the control group than those in groups E1 and E2 at 5th and 10th min during esmolol infusion and 10 min after extubation ($p<0.05$). The time for opening eyes in response to verbal commands was shorter in both esmolol groups compared to the control group($p<0.05$). The time for opening eyes spontaneously in Group E2 was shorter than it was in the control group($p<0.05$) whereas there was no difference in Group E1. Five patients in the control group (33.3%) needed antihypertensive agents while there was no need for such additional agents in GroupE1 and GroupE2. We think that both dose profiles can be used to prevent hyperdynamic state which occur during extubation without extending the recovery period, which will lead to an early postoperative clinical assessment.

Key words: Esmolol, extubation, anesthesia, remifentanil, recovery parameters

INTRODUCTION

The period of the emergence from general anesthesia or tracheal extubation is a hyperdynamic state in which increased oxygen consumption, catecholamine secretion, tachycardia and hypertension may be observed. This period lasts approximately 5-15 min (Miller *et al*., 1995). Although most of the patients tolerate this temporary state (Gal and Cooperman, 1975; Seltzer *et al*., 1980), the patients developing hypertension, cardiovascular or cerebrovascular disease preoperatively may suffer from severe cardiac or cerebral complications (Coriat *et al*., 1986; Elia *et al*., 1989). Therefore, the prevention of post-operative sympathetic response is very critical for the high risk patients in order to maintain haemodynamic stability and to reduce morbidity rate (Miller *et al*., 1995). Esmolol is a water soluble selective beta adrenoreceptor antagonist. Since it has a rapid onset and short duration of action (9 min), the use of esmolol in anesthesia is advantageous in the prevention of haemodynamic stress response.

This study is designed to determine the effects of two different infusion doses of esmolol which are used after the anesthesia given in combination with short-acting remifentanil and isoflurane on the prevention of haemodynamic response to extuabation and also on the recovery period.

MATERIALS AND METHODS

After obtaining the protocol approved by the Institute Ethics Committee and informed patient consent, 45 ASA (American Society of Anaesthesiologists) risk class I-II patients who were scheduled for elective lumbar disc surgery were randomly divided into three groups. The pregnant women and patients having a heart rate

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<60 bpm, systolic blood pressure <100 mmHg, serious hepatic, renal and cardiovascular diseases, congestive heart failure, atrioventricular block, sick sinus syndrome, drug allergy and past history of β-blocker intolerance, bronchospasm, asthma, chronic obstructive pulmonary disease, hematological disorders and receiving β-blockers and calcium channel blockers were excluded from the study.

The patients were allocated randomly into three groups. Group E1 (n=15) received 0.1 mg kg^{-1} min^{-1} esmolol infusion, Group E2 (n=15) received 0.2 mg kg^{-1} min^{-1} esmolol infusion and Group C (control group (n=15) received 0.2 mg kg^{-1} min^{-1} 0,9% serum physiological iv infusion.

The heart rate, noninvasive blood pressure, peripheral oxygen saturation (SpO_2) and the End-Tidal Carbon Dioxide ($ETCO_2$) pressure were monitored (Nihon KOHDEN, Multigas UNIT, AG-920 RK, Tokio).

After all patients were administered sodium thiopental 5-7 mg kg^{-1} iv bolus without any premedication, remifentanil infusion was started at the rate of 0.1-0.3 μg kg^{-1} min^{-1} and following the administration of 0.5 mg kg^{-1} atracurium endotracheal intubation was performed. Anesthesia was maintained with isoflurane (inspired 0.8-1.5%) in oxygen-air mixture (50:50). Mechanical ventilation was performed to keep $ETCO_2$ within 30-35 mmHg. Intravenous atracurium (0.1 mg kg^{-1}) was administered in order to maintain adequate muscle relaxation during surgery. Before the surgery was completed, all patients received tenoxicam 20 mg intravenously.

With closure of the skin, all anesthetic agents were discontinued. When spontenous breathing started, 0.025 mg kg^{-1} atropin and 0.04 mg kg^{-1} neostigmine were administered intravenously to antagonize the effect of muscle relaxing drugs. As determined before the groups received either esmolol (Brevibloc Premixed®; 10 mg mL^{-1}, Baxter, Baxter Healthcare Corporation, USA) or Serum Physiological (SP) infusion (infusion pump, Baxter Collegue, Canada). Esmolol and SP solutions were prepared without the knowledge of the person who would keep the records. Both Group E1 and GroupE2 patients received esmolol 0.5 mg kg^{-1} bolus dose for 4 min. Afterwards, Group E1 and Group E2 received maintenance esmolol infusions at the rate of 0.1 and 0.2 mg kg^{-1} min^{-1}, respectively. The infusion continued till 10 min after extubation. Group C received the same volume of 0.9% SP solution. When systolic blood pressure was found higher than180 mmHg, or more than 50% of elevations of systolic blood pressure according to control values was defined as hypertension and treated with additional antihypretensive, 0.1 mg bolus injections of glycerol trinitrate (Perlinganit® 10 mg mL^{-1}, Adeka) during or/and after esmolol or SP infusions. The extubation times and recovery periods were recorded. The recovery period was assessed according to opening eyes spontaneously or in response to verbal commands and orientation to place, time and person.

Statistical analyses were performed with SPSS for Windows 12.0. For parametrical data, one way Analysis of Variance (ANOVA) was used and Bonferroni correction was applied when there was a significant difference; for nonparametrical data, Kruskall Wallis test was used and when there was a significant difference Mann-Whitney U test was applied. For gender, side effects and ASA chi-square or Fisher's exact tests were used. In the statistical analyses $p<0,05$ was considered to be significant.

RESULTS

In our study, all three groups of patients were comparable with respect to their demography and the duration of anethesia and surgery (Table 1).

There was no difference in the intraoperative HR and MAP values among the groups. While the control group had higher HR than the groups E1 and E2 at 5 and 10 min of infusion ($p<0.05$), there was no difference between Group E1 and Group E2 (Fig. 1).

Table 1: The demographic data of the groups [(Mean±SD), (n)]

	Group C (15)	Group E1 (15)	Group E2 (15)
Age (year)	50.3±12.2	50.3±17.1	48.1±16.2
Weight (kg)	77.5±9.3	77.9±15.6	74.5±15.4
Height (cm)	168.3±8.2	165.4±8.3	166.3±10.5
ASA (I/II)	9/6	8/7	6/9
Gender (F/M)	8/7	7/8	7/8
Duration of anesthesia (min)	145.5±69.4	152.5±64.2	161.4±85.5
Duration of the surgery (min)	121.2±62.8	129.7±65.5	138.5±84.6

Table 2: The incidence of hypertension and hypotension and the need for antihypertensive [n, (%)]

	Group C (15)	Group E1 (15)	Group E2 (15)
	5 (33.3)*	-	-
Hypotension	-	1 (6.7)	-
Need for antihypertensive	5 (33.3)*	-	-

*p 0.05 : When the results of Group C were compared with those of Group E1 and Group E2

Table 3: Recovery periods, total infusion duration and extubation time (Mean±SD)

	Group C (15)	Group E1 (15)	Group E2 (15)
Oopening eyes in response to verbal			
C commands (min)	5.9±4.5†	2.1±1.5	1.8±1.4
OOpening eyes spontenously (min)	6.9±5.4*	4.0±3.1	2.8±1.8
Orientation to place (min)	8.7±5.8	6.5±3.9	4.7±3.2
Orientation to time (min)	9.6±6.2	7.2±4.3	5.4±3.4
Orientation to person (min)	9.4±6.4	6.9±3.9	5.4±3.4
EExtubation time(min)	6.1±3.6	5.5±2.3	5.4±2.5
Infusion duration (min)	16.1±3.6	15.5±2.3	15.4±2.5

*p 0.05 : When the results of Group C were compared with those of Group E1 and Group E2, † $p<0.05$: When the results of Group C were compared with those of Group E2

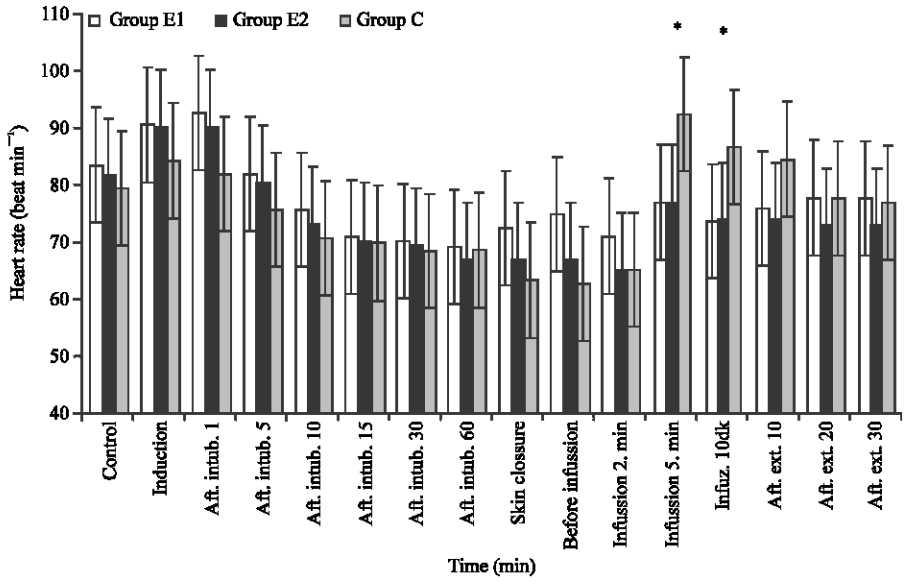

Fig. 1: The heart rates of the groups (Mean±SD)

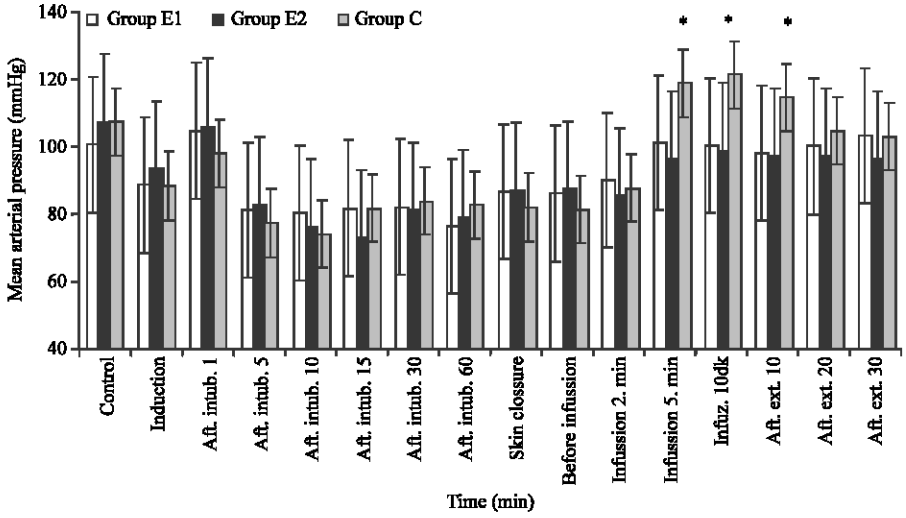

Fig. 2: The Mean Arterial Pressure (MAP) values of the groups (Mean±SD)

MAP values of Group C were found to be higher compared to the control rate at minutes five and ten of infusion and minute ten after extubation ($p<0.05$). There was no difference b/w Group E1 and Group E2 (Fig. 2).

Although during extubation period Group E2 had a stable haemodynomic state, five patients in Group C (33.3%) developed hypertension and so they were given additional hypertensive agents. One of the patients in Group E1 (6.7%) was observed to have hypotension (Table 2).

The time of opening eyes spontaneously was significantly longer in Group C than it was in Groups E1 and E2 ($p<0.05$) and there was no difference between group E1 and Group E2. The time of opening eyes in response to verbal commands was longer in Group C when compared to the Groups E1 and E2; however, the difference was found to be statistically significant between Group C and Group E2 ($p<0.05$) and there was no difference between Group E1 and Group E2. No difference was observed among the groups with respect to the orientation to place, time and person. All groups had the same extubation time, total esmolol and SP infusion periods (Table 3).

DISCUSSION

In this study, we observed that both dose profiles of esmolol prevented tachicardia and hipertension response to extubation without extending the recovery period, which enabled an early clinical assessment.

Tracheal extubation has been defined as the cause of temporary but serious blood pressure and HR elevations in 10-30 % of patients. Although cardiovascular stimulation appears to be unimportant in this period which lasts 5-15 min, there may be some unwanted and unexpected results in some groups of patients (Miller *et al*., 1995). Coriat *et al*. (1986) showed that there was a decrease from 55% to 45% in the ejection fraction after extubation in the patients with coronary arterial disease. Wellwood *et al*. (1984) indicated that the patients who had the cardiac index less than 3L/min/m^2 and who also encountered postoperative tracheal extubation stress after myocardial revascularization had a decrease in their cardiac performance and left ventricular compliance.

After brain surgery early neurological assessment is preferred. For this reason, the use of remifentanil, the analgesia with an effect of short duration, is considered to be advantageous (Guy *et al*., 1997). However, because the effect of remifentanil is of a short duration, it is considered that the hemodynamic fluctuations in early post-operative period may be more severe (Guy *et al*., 1997). The fact that 33.3 % of the patients in the control group who received remifentanil in our study needed antihypersensitive agents confirms this idea. In their study, comparing remifentanil with fentanyl, Guy *et al*. (1997) reported that although the group who received remifentanil had a faster recovery, more labetalol or hydralizine should be used to control the increase in SBP. The periods during and after the extubation haemodynamic balance should be kept stable in the risk patients who are desired to emerge from anesthesia early. For this reason, we aimed to study the effects of different infusions of esmolol on the haemodynamic response to the extubation performed during remifentanil-isoflurane anesthesia and also on the recovery period.

There are several methods and drugs used to provide haemodynamic stability during extubation and early post-operative period. Bidwai *et al*. (1978, 1979) and Wallin *et al*. (1987) reported that hypertension that may occur during extubation can be prevented with the topical or i.v. use of lidocain. Some other studies also indicate that the use of calcium channel blockers such as diltiazem, verapamil and nicardipine alone or in combination can reduce the hypertensive response to extubation (Nishina *et al*., 1995; Mikawa *et al*., 1996, 1997; Fujii *et al*., 1998, 1999; Toshinori, 2002). Fentanyl, which is often used in modern anesthesia to prevent hyperdynamic response to intubation, was administered to some normotensive patients by Nishina *et al*. (1995) and it was shown to reduce the hypertensive response to extubation. In some other studies by Nishina *et al*. (1996, 1997) i.v. infusion of Prostaglandin E1(PGE1) alone was reported to prevent hypertension but not tachycardia during extubation; however, the combination of PGE1 and lidocain prevented both hypertension and tashycardia. It has also been indicated that in order to blunt haemodynamic response, some vasodilator agents such as nitroprusside, nitroglycerin and hydralazine can be used, but there may be some side effects as reflex tashycardia and the an increase in the plasma renin activity (Gibson *et al*., 1988).

The increased adrenergic activity leading to hyperdynamic response during extubation period can be prevented by adrenergic receptor blocker agents. Dryden *et al*. (1993) observed that the haemodynamic response to extubation was less severe in the patients who received β blockers before coronary arterial surgery. Sharma *et al*. (1996) administered 100 and 200 mg bolus esmolol before induction to blunt haemodynamic response of the hypertensive patients to intubation and found out that both doses were effective in the prevention of hypertension and tachycardia, but suggested the application of 100 mg esmolol bolus as a more effective and safer method. In their study, comparing esmolol with labetalol, Muzzi *et al*. (1990) showed that both agents had the same effect to prevent the increase in the blood pressure during the recovery period after intracranial surgery.

Dyson *et al*. (1990) used esmolol in the doses of 1, 1.5 and 2 mg kg^{-1} 2-4 min before extubation and showed that all three doses were effective in the prevention of heart rate response to extubation, but 1 mg kg^{-1} esmolol did not prevent the increase in SBP compared with the other doses. They also indicated that 2 mg kg^{-1} esmolol caused severe hypotension, so that 1.5 mg kg^{-1} i.v. esmolol was enough to blunt the haemodynamic response to extubation.

It has been shown that the hyperdynamic state resulted from sympathetic stimulus after extubation lasts 5-15 min (Miller *et al*., 1995). Since the half life of esmolol is about 9 min, it is more appropriate to administer it through infusion for the best efficacy during hyperdynamic period (Gorczynski, 1985). Gibson *et al*. (1988) suggested the esmolol infusion to be continued till minute ten after extubation unless the HR <60 hb min^{-1} and the systolic blood pressure <100mmHg after brain surgery. In our study, we also continued the esmolol infusion till minute ten after extubation. The HR and blood pressure values of the control group decreased to baseline at 20 min after extubation and there was no statistically significant difference between Group E1 and Group E2.

In their study, to find the most effective dose for infusion, Lim *et al.* (2000) applied isoflurane-fentanyl-N_2O anesthesia. Esmolol 500 μg. kg^{-1} bolus was given during extubation after intracrannial surgery and it was followed by the doses of 0.1 and 0.2 mg kg^{-1} min^{-1} for 5 min after extubation. While 0.1 mg kg^{-1} min^{-1} dose could not prevent hypertension and tashycardia, 0.2 mg kg^{-1} min^{-1} dose was more effective. Although we used remifentanil-isflurane anesthesia, in the groups that received both 0.1 and 0.2 mg kg^{-1} min^{-1} infusion, tachycardia and hypertension could be well controlled.

In their study, comparing the efficacy of esmolol and alfentanil during extubation, Fuhrman *et al.* (1992) used 5 μg kg^{-1} alfentanyl bolus dose followed by normal saline infusion or 500 μg kg^{-1} esmolol followed by 300 μg kg^{-1} esmolol and showed that in the infusion of esmolol following the bolus dose could better control the increase in the systolic arterial pressure and heart rate that occur as a response to emergence and extubation. However, since Lim *et al.* (2000) indicated that they did not use 300 μg. kg^{-1} min^{-1} infusion dose because it caused 12% hypotension, we administered 500 μg kg^{-1} min^{-1} esmolol bolus and then used 0.1 and 0.2 mg kg^{-1} min^{-1} infusion doses. While only one of the patients (6.7%) who received 0.1 mg kg^{-1} min^{-1} had hypotension, the group who received 0.2 mg kg^{-1} min^{-1} was not observed to have hypotension. Grillo *et al.* (2003) used 0.5 mg kg^{-1} bolus dose of esmolol dose in fentanyl-desflurane-N_2O anesthesia and following it they used 0.3 mg kg^{-1} min^{-1} infusion during extubation and for 15 min after extubation.

Esmolol is an agent which has no analgesic effect, little sedative effect and no anesthesic effect alone (Gorczynski, 1985). Nevertheless, there are some studies suggesting that esmolol reduced the anesthetic requirement to blunt the haemodynamic response the skin incision (Johansen *et al.*, 1997, 1998). Johansen *et al.* (1997) showed that the esmolol infusion which was used in combination with propofol, N_2O and morphine anesthesia before induction reduced the need for anesthesia. After ending the anesthesia we used similar esmolol bolus and maintenance esmolol and observed that recovery period was shorter compared to the control group. This situation seems to contradict with the expected efficacy of β-blockers. White *et al.* (2003) used esmolol as an adjuvant during anesthesia to control acute haemodynamic responses in desflurane-NO_2 anesthesia and found that the emergence from anesthesia was quicker, post-operative opioid demand decreased, the time for their discharge was shorter and the side effects were seen less often. Although White *et al.* (2003)used desflurane anesthesia, we used isoflurane anesthesia and administered esmolol not as an adjuvant but during extubation and for 1 min after extubation and observed that discharge periods were shorter in the both doses of esmolol. We were unable to explain the mechanism of shorter recovery period in this study and we think that furher studies are needed to clarify this situation more clearly.

CONCLUSION

In conclusion, we think that the use of 0.5 mg kg^{-1} min^{-1} bolus dose of esmolol followed by esmolol infusions at the rate of 0.1 and 0.2 mg kg^{-1} min^{-1} in patients who received remifentanil-isoflurane combined anesthesia blunt the haemodynamic response to extubation and shorten the period of recovery while suppressing sympathetic response.

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