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Low-dose esmolol: hemodynamic response to endotracheal intubation in normotensive patients

Düşük Doz Esmolol: Normotansif Hastalarda Endotrakeal Entübasyona Hemodinamik Yanıt

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ABSTRACT

Purpose: Endotracheal intubation is a frequently utilized and highly invasive component of anesthesia that is often accompanied by potentially harmful hemodynamic pressor responses. The purpose of this study was to investigate the efficiency of a single pre-induction 1 mg/kg bolus injection of esmolol for attenuating these hemodynamic responses to endotracheal intubation in normotensive patients.

Material and methods: The study was composed of 100 randomly selected male and female patients between the ages of 18 and 60 that were scheduled for elective surgery and belonged to ASA grade I or II. Two minutes prior to intubation the control group received 10 mL of saline (n=50) and the experimental group received an injection of esmolol 1 mg/kg diluted to 10 mL (n=50). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and rate pressure product (RPP) were compared to basal values before receiving medication (T-0), during pre-induction (T-1), induction (T-2), intubation (T-3), and post-intubation at 1 (T-4), 3 (T-6), 5 (T-8), and 10 (T-13) minutes.

Results: Esmolol significantly attenuated the hemodynamic responses to endotracheal intubation at the majority of measured points. Attenuation of HR (10.8%), SBP (7.04%), DBP (3.99%), MAP (5%), and RPP (16.9%) was observed in the esmolol group when compared to the control group values.

Conclusions: A single pre-induction 1 mg/kg bolus injection of esmolol successfully attenuated the hemodynamic pressor response in normotensive patients. A significant attenuation of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was observed at the majority of measured time points in the esmolol administered group compared to the control group.

Key words: Esmolol, endotracheal intubation, hemodynamic response, attenuation

Introduction

It is well documented that laryngoscopy and endotracheal intubation following induction of anesthesia is commonly associated with hemodynamic changes due to due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation[1-5]. This increased sympatho-adrenal activity may frequently result in hypertension, tachycardia and arrhythmias[6-8]. This increase in blood pressure and heart rate are usually transitory, variable and unpredictable. Transitory hypertension and tachycardia are probably of no consequence in healthy individuals [9], but either or both may be hazardous to those with history diabetes, pre-eclampsia, myocardial insufficiency or cerebrovascular diseases[10-13].

Several attempts have been made right since 1960's using various techniques and pharmacological agents to attenuate these haemodynamic responses to laryngoscopy and tracheal intubation[14]. High and low dose of opioids[15,16], adrenergic blockers[17] direct acting vasodilators[16], calcium channel blockers[17-19] and lidocaine [20,21] were tried to blunt these responses with varying success. However, beta blockers have a special role in preventing the tachycardic and hypertensive response following the laryngoscopy and tracheal intubation, because of their ability to control the heart rate and their reliable antihypertensive properties.

Among the beta blockers, various agents like propranolol, labetolol, acebutolol have been tried for blunting hemodynamic responses to laryngoscopy and tracheal intubation[22-24]. But they had the disadvantage of delayed onset of action and prolonged duration of action, which resulted in instances of intraoperative bradycardia and hypotension. Hence there was a need for a short acting beta blocker which has an early onset and short duration of action. Esmolol is an ultra short acting beta blocker introduced into the clinical practice in the middle of 1980's, fulfilled these criteria of early onset and short duration of action[25,26]. Since then, several studies have already assessed the effectiveness of esmolol with positive results; however there is wide variation of opinions with regards to optimum dose, mode, and timing of delivery[10,27]. It is therefore the purpose of this study to investigate whether a single 1mg/kg bolus pre-induction injection of esmolol administered 5 min prior to intubation would significantly attenuate the hemodynamic response to endotracheal intubation in normotensive patients.

Materials and methods

After approval by the ethical committee of Mysore Medical College and Research Institute (Mysore, India) and informed consent from all patients, the following study was preformed. The study population consisted of one hundred randomly selected male and female patients ages 18-60 years that were scheduled for various elective surgical procedures and belonged to either ASA grade I or II. Patients also were required to be normotensive and Mallampatti class I or II. Persons having hypertension, Diabetes mellitus, heart rate less than 70 bpm, systolic blood pressure less than 100mm Hg, 1st, 2nd, or 3rd degree heartblock, a difficult airway, history of ingestion of a beta blocking drug within 24 hours, history of myocardial infarction within 3 months, history of bronchospastic disease, or those who had cardiac, coronary, renal, hepatic, cerebral, or peripheral vascular diseases were excluded from the study.

Study Design

Patients were randomly assigned to either a control group (n= 50) that received 10mL of normal saline 2 minutes prior to laryngoscopy and intubation or an experimental group (n= 50) that received an injection of esmolol 1 mg/kg diluted to 10 mL in normal saline 2 minutes prior to laryngoscopy and intubation. Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), and Mean arterial pressure (MAP) were recorded using a Siemens SC-7000 multichannel monitor for all patients before receiving the study drug (T-0), after receiving premedication during pre-induction (T-1), at induction (T-2), at intubation

(T-3), and after laryngoscopy and intubation at intervals of one min. (T-4), three min. (T-6), five min. (T-8), and ten min. (T-13). The Rate pressure product (RPP) was also calculated.

Protocol

During the evening prior to surgery each patient underwent pre-anaesthetic evaluation with special consideration for any conditions that would exclude them from the study. Later that night the patients were also premedicated with tab alprazolam 0.5 mg and tab ranitidine 150 mg. On the day of surgery an 18-gauge intravenous cannula was inserted and a Dextrose infusion with normal saline was started. The patients were then connected to the Siemens SC-7000 multichannel monitor and, after recording baseline HR, SBP, DBP, and MAP were further premedicated with gylcopyrolate 0.2 mg, midazolam 1 mg, and pentazocine 15 mg IV. Then, after preoxygenation for 3 min. via a face mask with Brains circuit, patients either received the control drug (group 1: 10 mL normal saline) or the study drug (group 2: esmolol 1mg/kg diluted to 10 mL in normal saline). Thiopentone 5 mg/kg as a 2.5% solution was used to induce anesthesia and succinylcholine 1.5 mg/kg IV was used to facilitate intubation one minute priop to laryngoscopy and intubation. Laryngoscopy and intubation were preformed 2 min. after patients received their study drugs and, after confirmation of bilateral equal air entry, the endotracheal tube was secured. Anesthesia was maintained using 66% nitrous oxide and 33% oxygen and, after patient recovery from succinylcholine, vecuronium 0.05 mg/kg was used as an additional neuromuscular blockade. HR, SBP, DBP, and MAP continued to be recorded for 10 min. with no additional surgical or other stimuli. Patient anesthesia was reversed using neostigmine 0.05 mg/kg IV and atropine 0.02 mg/kg IV.

Results:

The demographic characteristics of each group were similar (Table 1). There were no statistical differences observed with respect to number of patients in each group, sex ratio, weight, or age. A single pre-induction 1 mg/kg bolus injection of esmolol in a thiopentone/suxamethonium anesthetic sequence was observed to successfully attenuate the hemodynamic pressor response in normotensive patients resulting from endotracheal intubation.

Table 1: Study participants demographic data

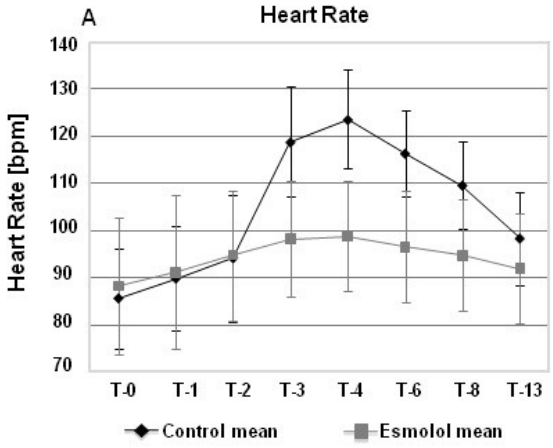
**Randomly selected ASA Grade I/II patients (n=50)*

	Gender ratio* (M/F)	Age** [years]	Weight** [kg]
Control	25 / 25	36.04±11.9/ 39.0±11.9	56.80±4.1/ 52.54±05.6
Esmolol	23 / 27	34.01±10.7/ 35.8±10.1	54.13±8.2/ 51.50±06.6

***Values represent means ± SD*

Heart rate (HR)

Attenuation of heart rate related hemodynamic response to tracheal intubation by a single 1 mg/kg bolus of esmolol was observed at all measured time points except at pre-induction – average 10.80% greater than the control group (Figure1A) and 10.42% from esmolol basal levels (Figure 1B). At pre-induction (T-1) (n= 100, t= 0.53, p=0.30) & induction (T-2) (t=0.27, p=0.39), there was no statistical difference in the heart rate was observed between esmolol and control groups. At intubation (T-3), however, the esmolol group had a highly significant mean heart rate at 19% below the control (t=9.48, P≤0.001). Further, significant attenuation was also observed 1 min after intubation (T-4) (t=12.22, P≤0.001), which was lower than the control value by 22%, 3 min after intubation by 19% (T-6) (t=10.72, P≤0.001), 5 min after intubation by 15% (T-8) (t=7.01, P≤0.001) and again at 10 min post-intubation the esmolol group was 7% lower than that of the control (T-10) (t=2.87, P≤0.005).



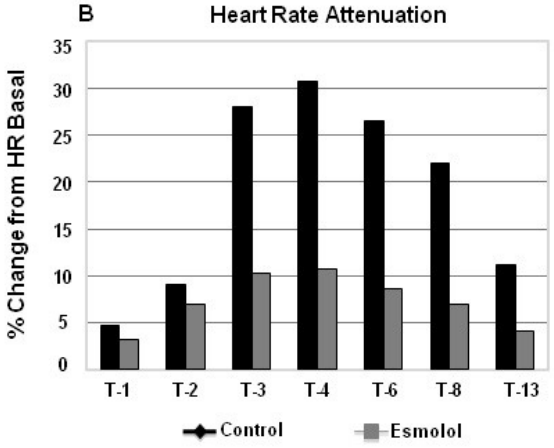
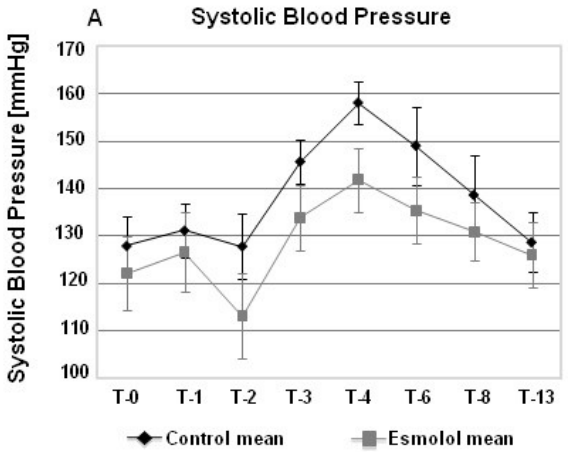


Figure 1. A&B

Systolic blood pressure (SBP)

Attenuation of systolic blood pressure was observed in the esmolol group with a 7.04 % average lower value than the control over all measured points (Figure 2A) and a 6.52 % lower value than the esmolol basal value (T-0) (Figure 2B). The greatest difference between measured points was at induction (T-2), where a 12% decrease from control levels was observed in the esmolol group (n=100, t=9.42, P≤0.001). At intubation (T-3), the esmolol group had a highly significant mean heart rate at 8 % below the control (t=10.00, P≤0.001). Further, significant attenuation was also observed 1 min after intubation (T-4) (t=14.54, P≤0.001), which was lower than the control value by 11%, 3 min after intubation by 10% (T-6) (t=8.47, P≤0.001), 5 min after intubation by 6% (T-8) (t=5.23, P≤0.001) and again at 10 min post-intubation the esmolol group was 2% lower than that of the control (T-13) (t=1.74, P≤0.05).



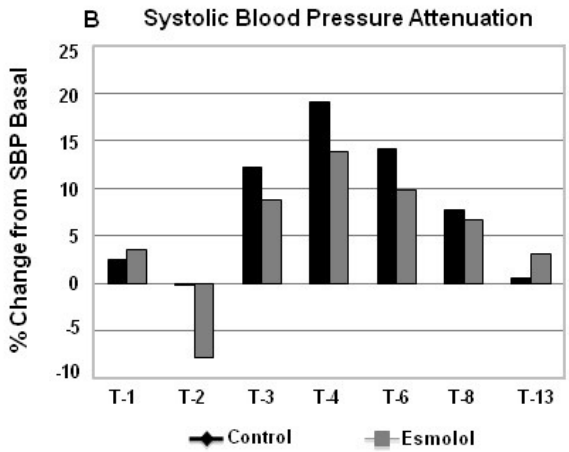


Figure 2. A&B

Diastolic blood pressure (DBP)

As with SBP, attenuation of the DBP pressor response to intubation in the esmolol group was observed at measured times from pre-induction through 5 min after intubation - on average 3.99% lower than the control (Figure 3A) and a 3.91% lower value than the esmolol basal value (Figure 3B). The greatest attenuation was observed at intubation with a 9% difference (T-3) (n=100, t=10.88, P≤0.001). This was preceded by no difference at pre-induction (T-1) (t=0.35, P=0.36) and a significant difference of 5.37% at induction (T-2) (t=3.12, P≤0.005). There was a 7% difference at 1min after intubation (T-4) (t=8.96, P≤0.001), a 5% difference at 3min (T-6) (t=3.95, P≤0.0001) and a 3% difference at 5min after intubation (T-8) (t=1.86, P≤0.05). No significant difference in the heart rate at 10 min after intubation was recorded. (T-13) (t=0.78, P=0.22).

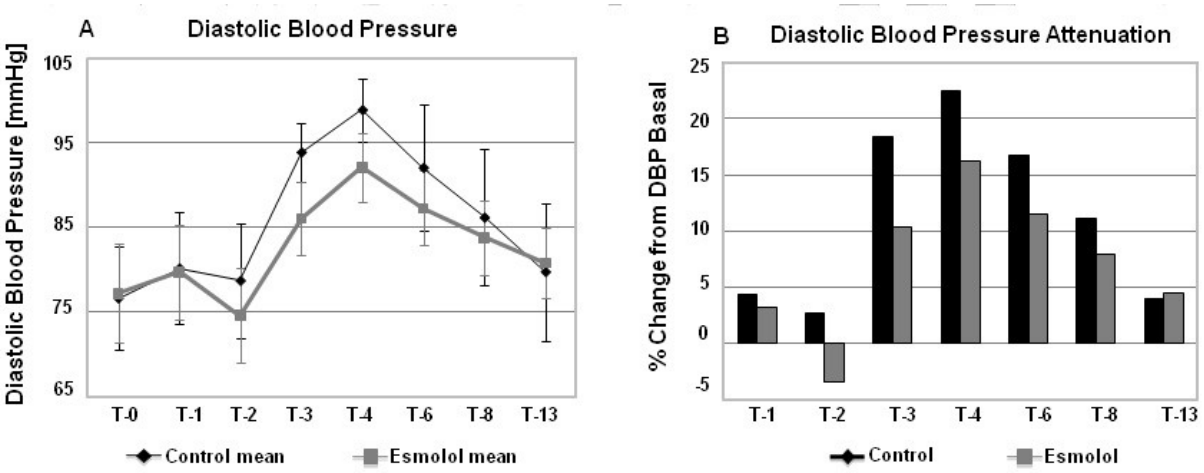


Figure 3. A & B

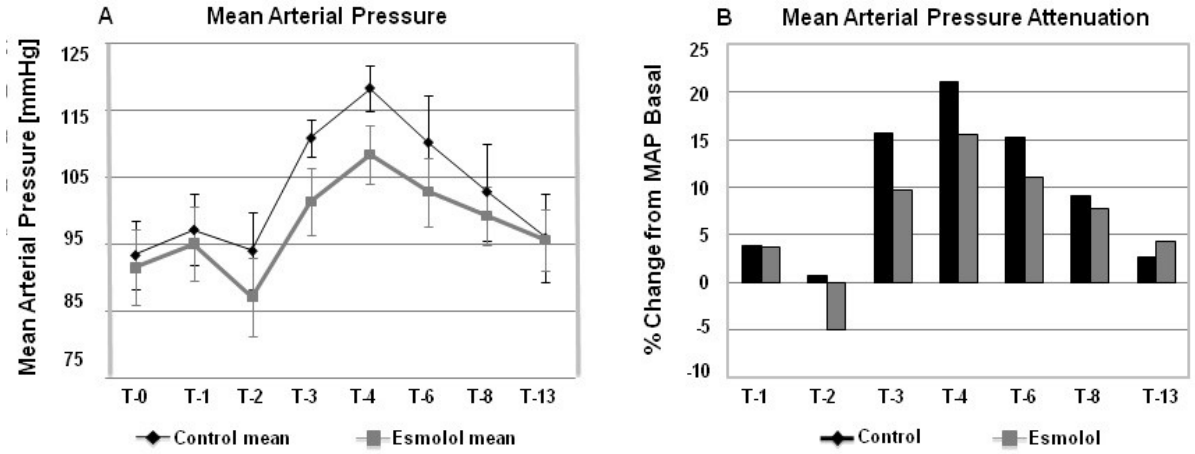


Figure 4. A & B

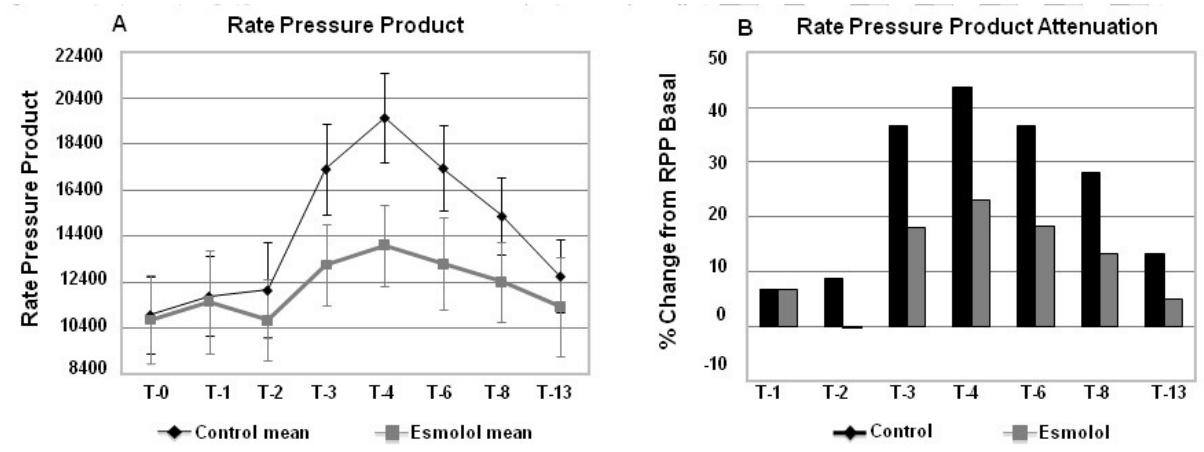


Figure 5. A & B

Mean arterial pressure (MAP)

Attenuation of MAP values was observed in the esmolol group with a 5 % average lower value than the control over all measured points (Figure 24A) and a 4.8 % lower value than the esmolol basal value (T-0) (Figure 4B). The greatest degree of attenuation was seen at both intubation (T-3) (n=100, t=12.4, P≤0.001) and 1min after intubation (T-4) (t=13.27, P≤0.001)

with a 9% difference observed at each time period. Pre-induction esmolol mean was 2% less than the control (T-1) (t=1.75, P≤0.05), followed by an 8% difference at induction (T-2) (t=5.54, P≤0.001). At 3min post-intubation there was a 7% difference (T-6) (t=5.92, P≤0.001) and at 5min the difference of 4% was recorded (T-6) (t=2.87, P≤0.005). However, No significant difference in the heart rate at 10 min after intubation was observed (T-13) (t=0.26, P=0.40).

Rate pressure product (RPP)

Attenuation of RPP values was observed, as expected, in the esmolol group with a 16.9% average lower value than the control over all measured points (Figure 5A) and a 16.6% lower value than the esmolol basal value(Figure 5B). The greatest attenuation was observed at 1min after intubation, with the esmolol group having a mean 33% below that of the control group (T-4) (n=100, t=16.5, P≤0.001). No significant difference at pre-induction between two groups was recorded (T-1) (t=0.63, P=0.27). Induction was 11.5% below (T-2) (t=3.97, P≤0.001) and intubation was 27% below control values (T-3) (t=12.3, P≤0.001). All post-intubation measurements were statistically significant. There was a 27% difference at 3min post-intubation (T-6) (t=12.1, P≤0.001), 21% at 5min post-intubation (T-6) (t=7.96, P≤0.001), and 11% at 10min post-intubation (T-13) (t=3.51, P≤0.001).

Discussion

A single pre-induction 1 mg/kg bolus injection of esmolol successfully attenuated the hemodynamic pressor response in normotensive patients. A significant attenuation of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was observed at majority of measured time points in esmolol administered group compared to control group. Ever since the hemodynamic response to laryngoscopy and intubation was first described as early as the 1940's[28], researchers have been searching for the most efficient medication to alleviate its potentially harmful effects. These effects include both a tachycardic and a hypertensive response that can be detrimental to patients with deteriorated health statuses. The pharmacodynamic properties of the anesthetic agent used for induction is one of the most important considerations when attempting to attenuate these responses[29]. In particular, agents that are fast-acting, have a short duration of action, and have few to no side effects are the most desirable. One agent that exhibits these properties is the beta-blocker esmolol.

Beta-blockers prevent the epinephrine stimulation of beta-adrenergic receptors, such as those on the heart and kidneys. When stimulated, these receptors produce a positive chronotropic and inotropic effect on the heart, thereby increasing heart rate and force of contraction. Simultaneously, rennin from the kidneys is released, a key enzyme in the regulation and increase of blood pressure. Therefore, antagonists of beta-receptors cause an antihypertensive effect, as well as minimizing tachycardia. Additionally, beta-blockers can exhibit antiarrhythmic effects which result from a sympathetic nervous system blockade[30]. Among beta-blockers, esmolol has a unique structure that makes it ideal for intubation studies. Its ester-methyl side chain makes fast-acting hydrolysis possible and therefore creates a rapid onset and short duration of action. These characteristics are ideal for drugs as prolonged use can cause undesirable side effects[31, 32]. Many studies evaluating the optimum dose and conditions for administering esmolol have been conducted with varying results. Doses as low as 0.2 mg/kg and 0.4 mg/kg have not been sufficient for attenuating either tachycardia or hypertension[33,34]. While doses as high as 2 mg/kg were sufficient but are more than likely to cause adverse side effects such as bradycardia and hypotension[27,35]. Other research has found that 1 mg/kg is successful at alleviating some hemodynamic responses but is less efficient at attenuating others, especially blood pressure[35,36]. This effect can sometimes be seen even with higher doses. Ugur et al, for instance, found that 1.5 mg/kg attenuated tachycardia but not hypertension[5]. Although there was some variation between the efficacy of esmolol on heart rate and blood pressure, our data supported that esmolol 1 mg/kg was

sufficient for attenuating both responses. On average there was attenuation at all measured points when compared to control values for HR (10.8%), SBP (7.04%), DBP (3.99%), MAP (5%), and RPP (16.9%). There may, however, be a complication in interpreting the MAP values because pre-induction values between the two groups were statistically different, suggesting that there may have been an inherent difference between the control and experiment groups' basal MAP values. If so, this difference could have contributed to the decreased values after induction and, therefore, it cannot fully be determined if esmolol aided in MAP attenuation. Other than MAP values, our results are supported by a selection of other research[37,38].

There are many possible reasons why our research better attenuated both tachycardia and hypertension, as opposed to other research utilizing a 1 mg/kg dose. For instance, sample selection may have played a role. We used a normotensive population in order to get a good baseline for the drug's general effects. Other studies, however, included patients with diabetes[36], coronary artery disease[38], and cigarette smokers [35]. It is possible that the deteriorated health statuses of the cigarette smokers was the reason that 1 mg/kg esmolol was not sufficient at attenuating all of the hemodynamic responses, while the same dose was adequate for our normotensive patients. In addition to alleviating the hemodynamic responses to intubation, our study suggests that esmolol 1 mg/kg is an optimal choice for intubation because there were no observed side-effects in either the control or experimental groups. This implies that, unlike higher doses of esmolol that can result in harmful side-effects[27,35] or lower doses that are insufficient[33,34], 1 mg/kg is a strong enough dose to attenuate hemodynamic responses and its fast-acting properties allow for a much lower risk of hypotension or bradycardia.

These fast-acting properties also make esmolol cost-effective. Although not a priority for developed countries, cost remains a key component in drug choice for nations with public health care. Not only does one have to consider the cost of the drug, but also its effects on other medical procedures. With a short-acting drug, concerns about post-surgery maintenance are minimized as there is less frequently needs to correct harmful side-effects. This fact alone can save money and expedite procedures, freeing up medical staff for more pressing issues[29].

In conclusion, a pre-induction 1 mg/kg bolus injection of esmolol given two minutes prior to intubation in 18-60 year-old normotensive patients of ASA physical status I/II is efficient as an early onset, short duration beta-blocker that successfully attenuates hemodynamic responses to intubation in a cost-effective manner and with no side effects.

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