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The Esmolol-Mivacurium Drug Interaction under Isoflurane Anaesthesia

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This prospective, randomized, double blind, placebo controlled study was designed to examine the safety and impact of extended esmolol infusion on plasma choline esterase (PChE) activity and mivacurium neuromuscular blockade and cardiovascular profile. Forty adult ASA I/II adult patients undergoing elective endo-urological surgery were included. Patients were randomly assigned to receive at induction either esmolol or saline infusion. All patients received fentanyl-propofol mivacurium (0.2 mg kg⁻¹) induction and isoflurane in oxygen maintenance of anaesthesia. Mivacurium infusion was adjusted to maintain the twitch response at 5-10% of the control. The PChE activity was more inhibited (by >2.5 times) in the esmolol group compared to the control group. The onset times were similar in the two groups. There was significant prolongation of mivacurium clinical duration (by 18.6%) and recovery index (6.67%) as well as, significant reduction of the total mivacurium consumption (by 24.1%) in the esmolol group compared to the control group. The heart rate and blood pressure in the esmolol group were significantly lower than those in the control group throughout the study period. This study demonstrate that esmolol infusion caused a moderate inhibition of the PChE activity resulting in moderate prolongation of the clinical duration and recovery index of mivacurium and reduction of its total dose consumption by infusion without the affecting the onset time. Caution is warranted if this combination is used in a patient with low PChE activity due to a disease, e.g., severe liver impairment or drugs, e.g., bambuterol.

Key words: Esmolol, mivacurium, plasma choline esterase, drug interaction, neuromuscular blockers

INTRODUCTION

Mivacurium has a short duration of action because of its rapid hydrolysis by plasma cholinesterase (PChE) (Lien *et al.*, 1994; Østergaard *et al.*, 2005). Several investigators have demonstrated an inverse relationship between PChE enzyme activity and duration of action of mivacurium indicating that patients with very low enzyme activity, irrespective of the cause, may exhibit a prolonged neuromuscular block following mivacurium (Østergaard *et al.*, 2005; Head-Rapson *et al.*, 1994, 1995).

Esmolol is a cardio-selective ultra-short acting beta adrenergic blocker. Its rapid total body clearance indicates that the blood esterase activity is the major factor responsible for its rapid breakdown (Volz-Zang *et al.*, 1994). Although the aryl esterase enzyme mediating the hydrolysis of esmolol is present in the cytosol of red blood cells and is distinct from plasma cholinesterase, yet, esmolol and its metabolite, due to their chemical structure may still inhibit PChE. Such an inhibition may potentiate the effects of drugs that are metabolized by PChE such as succinylcholine, mivacurium and procaine (Barabas *et al.*, 1986).

The ability of esmolol to inhibit PChE has been *in vitro* verified by Barabas *et al.* (1986). However, they failed to demonstrate significant inhibition of PChE when they *in vivo* tested esmolol in two different infusion regimen that lasted for 4 min each. One possible explanation for their inability to demonstrate significant PChE inhibition is the short duration of the esmolol infusion used in their study. They concluded that further investigation on the possible esmolol-mivacurium interaction is required (Barabas *et al.*, 1986). Since then, such interaction has been inadequately studied and publications on it are scarce and are mainly animal studies (Cheng *et al.*, 1995; Kim *et al.*, 1998).

Moreover, several investigators have demonstrated the anaesthetic and opioid sparing effects of an extended esmolol infusion and recommended that it should be a part of balanced anaesthesia particularly in the day-case setting since its use was associated with less opioids and anaesthetics consumption and less post-operative nausea and vomiting (PONV) (Smith *et al.*, 1991; Johansen *et al.*, 1997; Wilson *et al.*, 2004; Oda *et al.*, 2005).

Since mivacurium is the muscle relaxant of choice for short surgical procedures, many of which are now performed as day-cases, then studying the effects of extended esmolol infusion on its neuromuscular and haemodynamic effects is warranted. Therefore, this

prospective, randomized, double blinded, placebo controlled study was designed to examine the safety and impact of extended esmolol infusion (>30 min) on PChE activity, mivacurium-induced neuromuscular blockade and haemodynamic profile.

MATERIALS AND METHODS

This prospective randomized double-blind study was conducted at the Theodore Bilharz Research Institute between November, 2006 and April 2007. After obtaining the approval of the local Ethics Committee and informed patients' consent, forty adult ASA I/II patients undergoing elective endo-urological procedures for a bladder tumours or stones were randomly assigned (closed envelop technique) to either the esmolol group or the control group. Patients who had major systemic disease or personal and/or family history of an abnormal response to neuromuscular blocking agents were excluded. Patients who were pregnant, significantly overweight (greater than 30% of predicted weight), alcoholic, drug abusers, receiving cardio-respiratory-active or chemotherapy and/or radiotherapy or drugs that may affect neuromuscular transmission such as aminoglycosides, quinine, anti-epileptics or anti-histamines within one week prior to the study, were also excluded.

All patients received routine general examination and preoperative investigations including complete blood picture, serum creatinine, liver function tests and ECG (for patients aged 40 years or more). Sedative premedication was omitted. Following the establishment of 5 leads ECG, non-invasive blood pressure and oxygen saturation monitoring using S/5 anaesthesia monitor (Datex-Ohmeda, Helsinki, Finland), baseline readings were recorded and two intravenous cannulae were secured under local anaesthetic.

Following pre-oxygenation for 3 min, anaesthesia was induced using 2 µg kg⁻¹ fentanyl and propofol 2-2.5 mg kg⁻¹ and ventilation was assisted or controlled using isoflurane 1% in oxygen via a face mask and a circle circuit. Concomitant with anaesthesia induction, patients in the esmolol group received a loading dose of esmolol by infusion of 500 µg/kg/min for 2 min followed by an infusion of 200 µg/kg/min until the end of surgery. Patients in the control group received an equal volume of normal saline loading dose followed by an infusion of normal saline until the end of surgery as placebo. Either infusion was infused through a dedicated IV cannula. All used syringes and infusions were prepared by a colleague

anaesthetist not participating to the study and the investigator was unaware of the content of syringes and infusions.

Neuromuscular monitoring was established to monitor and record the evoked electrical muscle activity over the thenar muscles in response to ulnar nerve stimulation using the train-of-four mode of stimulation using the Datex Relaxograph NMT-100 Monitor (Datex, Finland). After stabilization, all patients received an initial dose of mivacurium 0.2 mg kg⁻¹ over 30 sec IV. Tracheal intubation was performed when complete muscle paralysis was achieved as measured by the Relaxograph.

Artificial ventilation of the lungs was performed using Datex-Ohmeda S/5 anaesthetic machine ventilator (Datex-Ohmeda, Helsinki, Finland) and was adjusted to maintain an end-tidal carbon dioxide concentration ranging between 32-36 mmHg using S/5 compact airway module M-CAiOVX attached to the S/5 anaesthesia monitor (Datex-Ohmeda, Helsinki, Finland). Anaesthesia was maintained with 0.8% end-tidal isoflurane concentration in oxygen and incremental fentanyl 50 µg as clinically indicated.

When the first response to TOF stimulation reached 25% of the control height, mivacurium infusion at 10 µg/kg/min was started and adjusted to maintain the twitch response at 5-10% of the control. The infusion was stopped approximately 10 min before the end of surgery.

Patients were allowed to have a spontaneous recovery after stopping the mivacurium administration. The mivacurium onset time (the time from injection to 95% block), clinical duration (time from end of injection of mivacurium to 25% recovery of the twitch response), recovery index (time from 25 to 75% recovery of twitch height) and total dose were recorded. Oropharyngeal suction and extubation were performed when the train of four ratio reached 75% recovery with no clinical evidence of inadequate recovery. In the recovery room, patients were given oxygen 3 L min⁻¹ via face mask and were observed for signs of residual curarization until discharged to the ward.

The heart rate (HR) and mean arterial pressure (MAP) readings were recorded at baseline and every 5 min throughout the procedure. If the MAP dropped below 60 mmHg, increments of ephedrine 6 mg every 3 min were given until MAP was maintained >60 mmHg. If the HR dropped below 50 beats min⁻¹, atropine 0.3 mg was given and repeated until the HR exceeded 50 beats min⁻¹.

From each patient a non haemolysed heparinized blood sample (3 mL) was collected for measurement of plasma cholinesterase at baseline and 30 min after

induction of anaesthesia. After separation, the plasma cholinesterase level and activity of the collected heparinized plasma was measured by the kinetic colorimetric method (Den Blawen *et al.*, 1983).

Statistical analysis: Normality of data was confirmed by One-Sample Kolmogorov-Smirnov test. Statistical analysis was performed using Chi square test, student's t-test and two-way analysis of variance for repeated measures on one factor where appropriate. Haemodynamic variables were analyzed using analysis of covariance (ANCOVA) test. All data analysis was carried out using the commercial statistical package SPSS version 10. A p-value of <0.05 was considered significant.

RESULTS AND DISCUSSION

There was no statistically significant difference (p>0.05) among the groups regarding the demographic data, ASA status, duration of surgery and preoperative laboratory investigations (Table 1, 2).

The measurement of the PChE level showed no statistically significant difference between the two study groups before and after induction of anaesthesia (Table 3). Compared to baseline levels, the post-induction PChE level in the control group was reduced by 2.8% while the PChE level was reduced by 9.2% in the esmolol group. This difference did not reach statistical significance. However, the PChE activity was significantly more inhibited (by >2.5 times) in the esmolol group compared to the control group (Table 3).

Table 1: The patients' criteria and duration of surgery

Patients' criteria	Control group (n = 20)	Esmolol group (n = 20)	p-value
Age (years)	42.8±8	40.1±9.6	0.340
Weight (kg)	69.8±8.5	66.8±9.8	0.307
Gender: Female: Male	8:12	7:13	0.864
Smoking:non-smoking	14:6	13:7	0.796
ASA status (I/II)	15/5	13/7	0.169
Duration of surgery (min)	66.8±14.8	64.1±15.1	0.571

Data are presented as Mean±SD unless otherwise indicated

Table 2: The pre-operative laboratory investigations

Laboratory investigations	Control group (n = 20)	Esmolol group (n = 20)	p- value
ALT (µ L ⁻¹)	23.60±6.50	23.00±4.80	0.741
AST (µ L ⁻¹)	24.90±3.20	24.30±4.80	0.644
ALK (µ L ⁻¹)	98.90±33.0	96.60±30.8	0.821
Bilirubin (mg dL ⁻¹)	0.70±0.26	0.74±0.20	0.588
Albumin (g dL ⁻¹)	3.40±0.52	3.10±0.47	0.072
Creatinine (mg dL ⁻¹)	0.77±0.30	0.72±0.23	0.557
Urea (mg dL ⁻¹)	25.00±6.70	24.10±6.80	0.675
Hg (g dL ⁻¹)	11.70±1.60	11.30±1.40	0.405

Data are presented as Mean±SD

Table 3: Changes in plasma cholinesterase level (U L⁻¹) and percentage of cholinesterase inhibition

Timing	Control group (n = 20)	Esmolol group (n = 20)	p-value (t-test)
Baseline	6619.10±1398.9	6308.8±1813.9	0.5482
Post-induction	6441.30±1380.2	5724.7±1643.1	0.1436
p-value (paired t-test)	0.624	0.751	
Inhibition of activity (%)	4.30±2.9	10.8±2.3*	<0.01

Data are presented as Mean±SD. *p<0.01 compared to control group

Table 4: Neuromuscular monitoring data in the control and esmolol groups

Neuromuscular data	Control group (n = 20)	Esmolol group (n = 20)	p-value
Onset time (min)	2.4±0.8	2.2±0.3	0.301
Clinical duration (min)	15.6±4.3	18.5±2.9*	0.016
Recovery index	6.0±0.6	6.4±0.4*	0.018
Total dose of mivacurium (mg)	31.9±6.2	24.2±7.6¶	0.001

Data are presented as Mean±SD. * p<0.05 compared to control group, ¶: p<0.01 compared to control group

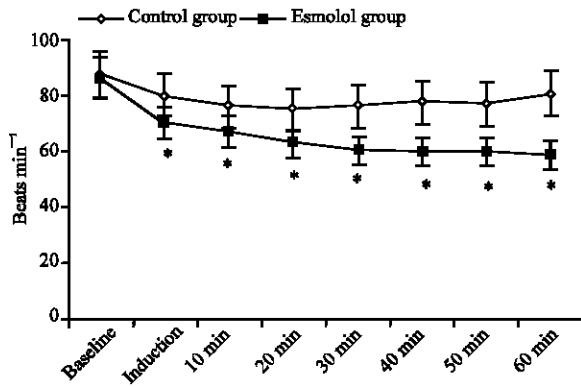


Fig. 1: Changes in the heart rate. Data are presented as Mean±SD. *p< 0.001 compared to the control group

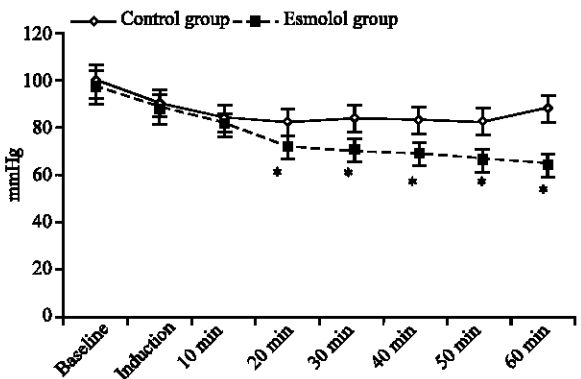


Fig. 2: Changes in the mean arterial pressure. Data are presented as Mean±SD. * p<0.001 compared to the control group

The onset times were not significantly different between the two groups (Table 4). However, the clinical duration was significantly longer (18.6%) and the total

dose of mivacurium was significantly reduced (by 24.1%) in the esmolol group compared to the control group (Table 4).

Similarly the recovery index in the esmolol group was modestly prolonged by 6.67% compared to the control group (Table 4).

Following anaesthesia induction and the start of the test drug infusion, the HR in the esmolol group was significantly slower than that in the control group throughout the study period except at the baseline reading (Fig. 1).

The MAP in the esmolol group was consistently lower than the corresponding reading in the control group throughout the study period. However, this difference reached statistical significance at the 20 min post-induction reading and remained significantly different until the end of the study period (Fig. 2).

None of the patients exhibited undue bradycardia or hypotension requiring treatment with either atropine or ephedrine, respectively.

The results of this study demonstrate that an extended esmolol infusion caused a significant inhibition of the PChE activity resulting in moderate prolongation of the clinical duration of mivacurium and reduction of its total dose consumption by infusion and modest prolongation of the recovery index without the effecting the onset time. Moreover, haemodynamic stability was achieved at a lower HR and MAP without undue hypotension or bradycardia.

The ability of some peri-operative drugs to inhibit PChE has been well established and it varies from minimal, e.g., metoclopramide (3%), to severe, e.g., bambuterol (90%) inhibition of PChE (Skinner *et al.*, 1999; Østergaard *et al.*, 2000; Motamed *et al.*, 2002). The inhibition of PChE activity observed in this study (10.4%) following esmolol administration is consistent with that reported by Kim *et al.* (1998) in rabbits (13%).

However, our results differ from those of Barabas *et al.* (1986), who reported marked *in vitro* PChE inhibition by esmolol but could not demonstrate significant inhibition of PChE *in vivo* using a dosing regimen similar to ours (esmolol loading dose of 500 µg/kg/min for 2 min followed by an infusion of 200 µg/kg/min). This discrepancy is hardly surprising since they assessed PChE activity after only 4 min of using this regimen, while we assessed it after 30 min.

The impact of such reduction in PChE activity observed in this study was a moderate prolongation of the duration of action of the intubating dose of mivacurium (by 18.6%) and a moderate reduction of mivacurium infusion requirement (by 24.1%) and a modest prolongation of the recovery index of mivacurium (by 6.67%). These observations confirm the findings of

several other investigators who demonstrated that in phenotypically normal subjects, a decreased PChE activity, whether due to physiological variation, disease or drug therapy, prolongs the duration of action of mivacurium and prolong the recovery index (Østergaard *et al.*, 2000, 2002, 2005).

However, taking in account of the very short elimination half time of esmolol and the short duration of action of mivacurium, it is unlikely that the statistically significant esmolol-induced effects on mivacurium neuromuscular blockade would be of significant major clinical consequences unless they are both administered to a patient with low PChE activity due to a disease, e.g., severe liver impairment or drugs, e.g., bambuterol.

Ezri *et al.* (2003) have demonstrated that a single bolus dose of esmolol (0.5 mg kg^{-1}) reduces the heart rate by 13%, the cardiac output by 31.25% and prolonged the onset time of rocuronium 0.6 mg kg^{-1} by 31% (from 87 to 114 sec). Such prolongation was not seen in this study using mivacurium instead of rocuronium. It is likely that any tendency of esmolol to prolong the mivacurium onset time secondary to its effect on heart rate and cardiac output is antagonised by the increase in the free blood concentration secondary to PChE inhibition. This is consistent with the findings of other investigators, who demonstrated that the onset time is inversely proportional to the dose (blood concentration) of neuromuscular blocking agents (Healey *et al.*, 1986; Kopman, 1989; Wright *et al.*, 1999). In addition, the difference in the esmolol dose and mode of administration in the two studies could also account, at least partially, for the lack of influence of changes in haemodynamic on the onset of mivacurium.

The addition of an esmolol infusion to the anaesthetic technique provided a reduction of both the HR and MAP throughout the surgical procedure. This effect is of paramount importance for patients with ischaemic heart disease in whom increases in HR and MAP subsequently increase myocardial oxygen demand and may jeopardize the myocardial oxygen demand-supply balance. Such reduction of both the HR and MAP is also important for decreasing blood loss and transfusion requirement which in turn is of particular importance to cancer patients undergoing surgery as it reduces cost, risk of transfusion reactions and risk of transfusion-related immuno-modulatory effects namely, tumour recurrence, postoperative infections, allograft survival and auto-immune disease (Strumper-Groves, 2006).

The use of esmolol was initially recommended for blunting of adrenergic responses to several peri-operative stimuli, including the pressor response to laryngoscopy

and intubation, intra-operative hypertension and tachycardia, emergence and extubation (Miller *et al.*, 1991; Singh *et al.*, 1992; Bakan *et al.*, 2006; Kovac and Masiongale, 2007).

In recent years, there has been growing interest in the use of esmolol as part of balanced anaesthetic technique since an extended esmolol infusion has been shown to produce a dose-dependent reduction in the anaesthetic requirement during propofol-morphine-nitrous oxide anaesthesia (Johansen *et al.*, 1997) and has been proposed as an alternative to alfentanil during propofol-nitrous oxide anaesthesia in patients receiving neuromuscular blocking agents (Smith *et al.*, 1991). It also suppresses the bispectral index response to tracheal intubation during sevoflurane anaesthesia (Oda *et al.*, 2005) and reduces the propofol dose requirement for anaesthesia induction (Wilson *et al.*, 2004).

Another advantage to the use of esmolol as part of a balanced anaesthetic technique is a reduction in PONV due to its opioid sparing effect resulting in earlier fulfilment of home discharge criteria (Smith *et al.*, 1991; Johansen *et al.*, 1997; Coloma *et al.*, 2001; Collard *et al.*, 2007). The reduction of PONV is of particular importance for day-surgical patients since it increases health care costs due to hospital admissions and accounts for 0.1-0.2% of unanticipated admissions which is quite significant in a place like the United States where more than 31 million patients undergo ambulatory surgery each year (Gan *et al.*, 2007) or in developing world where the resources are limited.

These observations together with the fact that both mivacurium and esmolol have a short duration of action, usually are administered by infusion and are both often used in the day-case setting, increase the significance of studying their interaction so that they could be utilized in a safe and efficient manner.

CONCLUSION

The results of this study demonstrate that an extended esmolol infusion caused a moderate inhibition of the PChE activity resulting in moderate prolongation of the clinical duration of mivacurium and reduction of its total dose consumption by infusion and modest prolongation of the recovery index without the affecting the onset time. However, caution is warranted if this combination is used in a patient with proven or suspected low PChE activity, e.g., liver impairment.

Moreover, the addition of an esmolol infusion to the anaesthetic technique provided cardiovascular stability at a lower heart rate and blood pressure. These two findings

confirm the safety and usefulness of this combination in this type of surgery and describe the clinical effects of esmolol-mivacurium interaction and therefore, making its clinical use in the general surgical population, especially in the day-case setting, advantageous.

Further studies on a large number of patients are required to appropriately evaluate the side-effects profile of the esmolol-mivacurium combination.

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