

Prophylactic Esmolol Infusion for the Control of Cardiovascular Responses to Extubation after Intracranial Surgery

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Abstract

Introduction: Emergence from general anaesthesia and extubation are often accompanied by significant surges in heart rate and blood pressure. To document these changes and the efficacy of low-dose beta-blocker infusions in ameliorating these rises, we undertook a descriptive dose-ranging study comparing the use of esmolol to placebo in patients emerging from neuro-anaesthesia. **Materials and Methods:** Thirty-six patients undergoing intracranial surgery were randomised to receive saline, esmolol 100 µg/kg/min or 200 µg/kg/min infusions. The number of patients developing severe hypertension or tachycardia in each group was compared using Fisher's exact test. **Results:** Systolic blood pressure (SBP) and heart rate (HR) increased in all 3 groups during emergence and peaked at extubation. The proportion of patients with severe tachycardia or hypertension was reduced from 92% in the placebo group to 40% ($P = 0.02$) and 8% ($P = 0.001$) in the low and intermediate dose esmolol groups, respectively. Results were better in the intermediate dose group but the difference was not statistically significant. Two patients from the esmolol infusion groups required supplemental medication for bradycardia. **Conclusion:** Severe hypertension or tachycardia occurs in 92% of patients during extubation following neuro-anaesthesia and warrants the consideration of routine prophylaxis. Prophylactic esmolol infusion for the control of haemodynamic disturbances during extubation is feasible and safe. A modest level of obtundation is evident at 100 µg/kg/min but a rate of 200 µg/kg/min may prove to be more effective.

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Introduction

Both intubation and extubation are processes associated with blood pressure and heart rate flux.^{1,2} While many studies have been carried out on the changes associated with intubation,³⁻⁵ the frequency and magnitude of the changes associated with extubation are less well documented. Patients undergoing intracranial surgery, in particular, may be at greater risk as the extubation process is likely to be longer and cerebral auto-regulation of blood flow is additionally impaired. Standard anaesthetic practice in dealing with these changes is still largely reactive in nature with the administration of intravenous boluses of a short-acting beta-blocker, e.g. esmolol, on occurrence. In our institution, the practice is to give an esmolol bolus for increases of systolic blood pressure (SBP) or heart rate (HR) in excess of 30% to 40% above the patient's baseline levels. However, prophylactic continuous beta-blocker infusions may be a better alternative if the rise in blood

pressure and heart rate is commonly encountered in patients undergoing anaesthesia. We report here the changes in systolic blood pressure (SBP) and heart rate (HR) in patients emerging from intracranial anaesthesia and compared them against similar patients receiving low or intermediate dose esmolol infusion as prophylaxis against these changes.

Materials and Methods

The study is a limited dose-ranging study of the efficacy of 2 esmolol infusion rates compared against placebo in reducing the rise of SBP and HR associated with emergence from anaesthesia in patients undergoing intracranial surgery.

After hospital ethics committee approval and informed patient consent, 36 ASA I and II patients scheduled for elective craniotomy under general anaesthesia and tracheal intubation were enrolled in the study. Exclusion criteria included patients with previous history of congestive cardiac

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failure, heart block, bronchial asthma and patients on beta blockers.

General anaesthesia was induced with fentanyl 2 to 3 µg/kg and thiopentone 3 to 5 mg/kg. Tracheal intubation was facilitated with 0.5 mg/kg atracurium. General anaesthesia was maintained with nitrous oxide, oxygen and isoflurane; muscle relaxation was maintained with atracurium infusion; and analgesia was maintained with morphine. No morphine was given within 1 hour of extubation. Total dose of morphine did not exceed 0.15 mg/kg in all patients. All patients were monitored with lead II of the ECG, pulse oximeter, end-tidal CO₂, anaesthetic agent monitor and direct arterial blood pressure. Intraoperatively, SBP and HR were maintained within 10% of baseline levels by varying the concentration of isoflurane up to 1 MAC. No anti-arrhythmic or intravenous anti-hypertensive agents were employed. Ten minutes before the end of surgery, isoflurane was turned off. At the end of surgery, nitrous oxide was discontinued and muscle relaxation was reversed with neostigmine and glyco-pyrolate. Patients were extubated when awake and responsive to call.

The patients were randomly assigned into 3 groups of 12 patients each. Patients in the 2 esmolol groups received an intravenous esmolol bolus of 500 µg/kg, followed immediately by esmolol infusions at 100 µg/kg/min and 200 µg/kg/min in the low and intermediate dose groups respectively. The doses were chosen as a previous study using 300 µg/kg/min was associated with a 12% incidence of hypotension.⁶

Patients not receiving esmolol received a saline bolus and infusion instead. Apart from the initial infusions, the conduct of anaesthesia proceeded according to our usual practice. The drugs were given at the start of emergence and the infusions were stopped 5 minutes after the trachea

was extubated. Emergence was defined as the time when isoflurane was turned off to the time when the trachea was extubated. SBP and HR were measured at 1 minute intervals from time 0 (start of emergence) to 10 minutes after esmolol was stopped and compared to their baseline preoperative levels. The baseline SBP and HR was taken to be the mean of 2 separate readings taken on admission and the pre-anaesthesia consultation round a day before surgery.

SBP and HR were observed by an assistant not involved in the administration of the infusions. If hypertension or tachycardia was severe (SBP >200 mmHg/HR >120/min or >40% above the baseline, whichever was lower) and sustained beyond 1 minute in any of the 3 patient groups, escape medication comprising IV bolus esmolol 500 µg/kg was initiated and given by the assistant. Patients receiving escape medication were considered treatment failures and were excluded from further data analysis.

The proportion of patients in the 3 patient groups with severe haemodynamic changes were compared using Fisher's exact test⁷ (pair-wise testing, 2-tailed *P* values less than 0.05 were taken to be statistically significant).

Results

Thirty-six patients were enrolled into the study. The pre-study clinical data for patients in the 3 treatment groups are given in Table I. The mean baseline SBP, HR, time to reversal and time to extubation were approximately comparable in the 3 treatment arms.

Mean SBP and HR progressively increased at each stage of the extubation process, peaking at extubation in all 3 groups (Figs. 1 and 2). The increases were much greater in the placebo group, whereas mean SBP and HR were generally kept within ± 20% of baseline levels in both

TABLE I: PATIENT CHARACTERISTICS FOR EACH OF THE 3 TREATMENT GROUPS

	Placebo	Esmolol-100	Esmolol-200
Number	12	12	12
Type of surgery	9 excision of tumour, 1 clipping of aneurysm, 1 abscess drainage, 1 insertion of VP shunt	8 excision of tumour, 1 clipping of aneurysm, 1 epilepsy surgery, 2 decompression of trigeminal nerve	9 excision of tumour, 1 clipping of aneurysm, 1 epilepsy surgery, 1 elevation of depressed fracture
Male/Female	4/8	8/4	5/7
Median age [range] (years)	57 [25 to 74]	35 [27 to 67]	28 [21 to 67]
No. hypertensive	3	2	2
Mean wd HR (SD) (bpm)	70.8 (11.9)	72.4 (6.9)	70.4 (8.1)
Mean wd SBP (SD) (mmHg)	129 (15)	139 (21)	124 (12)
Mean time to reversal (SD) (min)	11 (4.1)	11.5 (3.6)	11.1 (2.9)
Mean time to extubation (SD) (min)	16 (4.0)	17.7 (3.9)	17.7 (4.9)

VP: ventriculo-peritoneal; wd: ward; HR: heart rate; SBP: systolic blood pressure; SD: standard deviation

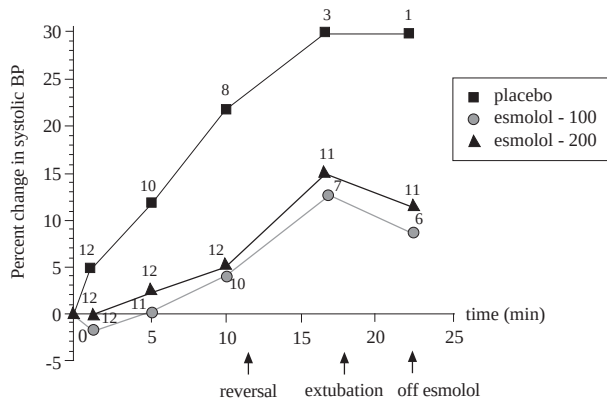


Fig. 1. Percentage change in systolic blood pressure with time from start of emergence. Two patients from the esmolol-100 group developed bradycardia and were excluded from further data analysis (1 patient soon after the bolus dose and the other before reversal could be initiated). The figures above each point indicate the number of patients remaining within the group.

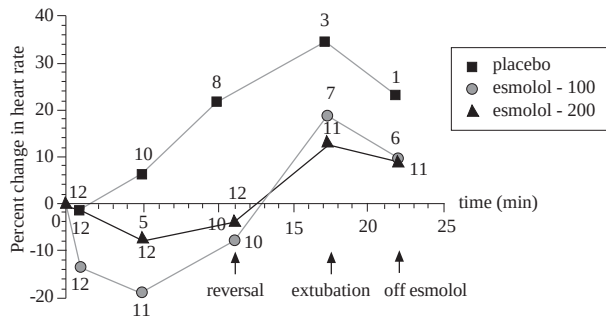


Fig. 2. Percentage change in heart rate with time from start of emergence. Two patients from the esmolol-100 group developed bradycardia and were excluded from further data analysis (1 patient soon after the bolus dose and the other before reversal could be initiated). The figures above each point indicate the number of patients remaining within the group.

esmolol groups throughout emergence. The actual magnitude of the increase in SBP and HR is, however, likely to be even higher than that indicated in the figures as the subsequent exclusion of patients who had received escape medication constitutes a censoring effect. The number of patients requiring escape medication is highest

in the placebo group. Consequently the censoring effect is likely to be greatest in the placebo group as well.

Table II shows that 92% (11 patients) of the patients receiving standard anaesthesia had severe haemodynamic changes requiring the administration of escape therapy as compared to 40% (4 patients) in the low dose and 8% (1 patient) in the intermediate dose esmolol infusion groups. The difference between placebo and either esmolol group was significant (95% CI for the difference was 15.3% to 88.0% for the low and 58.0% to 106.7% for the intermediate dose groups, respectively). Though a trend towards better control was seen in the intermediate dose group, the efficacy of low dose esmolol infusion was not statistically different from that in the intermediate dose group.

Esmolol infusions were generally well tolerated. With the exception of 2 patients from the low dose group who had significant bradycardia soon after the loading dose was given, emergence and extubation proceeded smoothly in the other patients. Esmolol infusion was stopped in these 2 patients and IV atropine was administered. Neither of them became hypotensive however, and both patients had subsequent smooth recoveries. Neither bronchospasm nor heart block was encountered.

Discussion

Excessive swings in blood pressure have long been a cause of concern in anaesthesia. An autopsy series of maternal deaths from eclampsia showed cerebral haemorrhages and cerebral oedema to be present in 57% and 18% of patients, respectively.⁸ The processes of intubation and extubation can impose significant additional stresses on patients already at risk. Hodgkinson et al⁹ reported a rise in mean arterial pressure of 45 mmHg with intubation as well as extubation in pre-eclamptic patients undergoing general anaesthesia, suggesting a place for short-acting hypotensive agents to be used during these 2 processes.

Neurosurgery is no less an area of concern than pre-

TABLE II: NUMBER OF PATIENTS DEVELOPING HAEMODYNAMIC DISTURBANCES DURING EMERGENCE

	Placebo	Esmolol-100	Esmolol-200
Total number of patients	12 (100)	10* (100)	12 (100)
No. with stable systolic blood pressure and heart rate (%)	1 (8.3)	6 (40)	11 (91.7)
No. developing severe hypertension (%)	6 (50)	0	1 (8.3)
No. developing severe tachycardia (%)	10 (83.3)	4 (40)	0
No. developing severe hypertension and/or tachycardia (%)	11 (91.7)	4 (40) ^a	1 (8.3) ^{b,c}

Fisher's exact tests of the difference in proportions of the 3 groups developing severe haemodynamic changes were significant between the placebo and either esmolol group. There was no significant difference between the 2 esmolol groups.

* Two patients in the esmolol-100 group developed bradycardia soon after esmolol was started and were excluded from analysis.

^a $P = 0.02$; placebo versus esmolol-100

^b $P = 0.001$; placebo versus esmolol-200

^c $P = 0.135$; esmolol-100 versus esmolol-200

eclampsia and a number of studies on the prophylactic use of hypotensive agents during intubation have been conducted. Their appropriateness during extubation is, however, less well reported.¹⁰⁻¹²

Our study indicates that hypertension and tachycardia are frequent occurrences during extubation in patients undergoing intracranial surgery. Gibson et al⁶ reported 91% of their patients undergoing extubation experience rises in blood pressure of at least 20% above the baseline levels. The mean maximal increase in SBP among patients from the placebo group was 38.1% with a mean maximal increase in HR of 53.4%. Tachycardia is as pernicious as hypertension, but is less frequently addressed. The study by Slogoff and Keats¹³ indicates that tachycardia, more than hypertension or hypotension, is a direct contributor to the development of perioperative myocardial ischaemia. The proportion of patients affected and the magnitude of the rise are grounds to consider the need for prophylactic measures during emergence in all patients undergoing intracranial surgery.

Methods to obtund this increase in blood pressure during emergence have ranged from extubating the patient “deep” to the use of lignocaine, vasodilators, narcotics and beta-adrenergic blockers. Following intracranial surgery however, the method chosen should not affect cerebral awakening or assessment of neurological status. Beta-adrenergic blockers, e.g. esmolol and labetalol, are possibly the drugs of choice^{6,14,15} as they fulfil the above criteria and additionally, have no significant effects on intracranial pressure or cerebral blood flow. The use of esmolol, a short-acting beta-adrenergic blocker, has been widely studied in anaesthesia and has been shown to be effective in obtunding both hypertension and tachycardia when given as a bolus⁵ as well as an infusion.¹⁶ Much of this data were collected on patients during intubation. The period of cardiovascular stress during emergence however, takes place on a background of lightening, not deepening, anaesthesia and is more prolonged. The efficacy of any proposed prophylactic measure during extubation should therefore be verified. The most frequently reported adverse effect following esmolol is hypotension.¹⁷ Continuous infusions are likely to be safer and more appropriate than intravenous boluses, especially in neuro-surgical patients. Apart from the complications associated with large intravenous boluses, the mean duration of time required for extubation in our patients was 16 to 18 minutes, considerably longer than the 9.2 minute half-life¹⁸ reported for esmolol.

Our present data indicate that low dose esmolol infusion (100 µg/kg/min) will obtund, though not prevent, the development of hypertension and tachycardia. Although a trend towards better control at a 200 µg/kg/min dose is

discernable, the difference in the reduction of severe haemodynamic disturbance between the 2 esmolol groups is not statistically significant. This is probably a reflection of the small sample size in the present study. Esmolol is well reported to have a dose-dependent effect and an earlier study⁶ using 300 µg/kg/min infusion enabled a greater attenuation of the changes in SBP and HR during emergence. The residual incidence of 33% severe haemodynamic disturbance for the low dose group in our study would not be considered adequate obtundation, but a bigger study is required to determine if the intermediate dose is indeed the optimal dose for prophylactic use.

Apart from the 2 patients with bradycardia however, none of the other patients developed any significant adverse effects. Bradycardia with esmolol is likely to be a dosage-related effect.¹⁷ The 2 patients who developed bradycardia were, however, from the lower esmolol dose group. None of the patients from the 200 µg/kg/min group became bradycardic. Bradycardia is most likely soon after the loading dose and both patients developed bradycardia before reversal was initiated. Of the 2 patients, bradycardia in 1 patient occurred at 12 minutes and in this patient at least, may have resulted from a factor other than esmolol. Bradycardia can also possibly result from vagal reflexes brought about by positional changes of the head in preparation for extubation.

Labetalol, a combined alpha and beta antagonist, is an alternative agent¹⁴ to the use of esmolol during extubation. It has been shown to be as effective as esmolol in treating hypertension following intracranial surgery but with a higher incidence of bradycardia. This is possibly a reflection of its longer half-life in the circulation. As labetalol is less cardio-selective than esmolol, it may also provoke bronchospasm.

The number of patients in our series is small. Despite randomisation, the median age of the patients in the placebo group was higher than those in the esmolol infusion groups. Though this may be a cause for bias, the effect is possibly small as the prevalence of hypertension and baseline SBP levels in the 3 groups were similar.

Conclusion

Routine prophylaxis against the development of severe haemodynamic disturbance during emergence is a worthwhile consideration for all patients undergoing intracranial surgery. Esmolol infusion obtunds the increase in SBP as well as HR and works well as a prophylactic agent. The 200 µg/kg/min esmolol infusion dose is safe with minimal adverse effects. A bigger study is required to determine if this dose offers the optimal level of control required.

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