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Esmolol as an anaesthetic adjunct in ambulatory surgery

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The aim of this study was to compare the efficacy of esmolol and fentanyl as anaesthetic adjuncts. Forty healthy patients presenting for laparoscopic tubal fulguration were randomly assigned to either an esmolol or fentanyl protocol, as part of a nitrous oxide/muscle relaxant anaesthetic technique. Blood pressure and heart rates, measured pre- and post-induction and intubation, showed no significant differences nor did the times of return of cognitive function and extubation respectively. Patients from the esmolol group were both ambulatory and discharged significantly sooner than the fentanyl group. The incidence of nausea and urinary retention, combined as adverse recovery room events were significantly higher in the fentanyl group. Esmolol proved to be a satisfactory substitute for narcotics in a nitrous oxide/relaxant anaesthetic technique and was associated with shorter times to ambulation and discharge.

Key words: Ambulatory surgery, anaesthetic adjuncts, esmolol, fentanyl

Introduction

The therapeutic use of pharmacologically active substances tends to evolve from the original intent as dictated by experience and research. For example propranolol (Inderal) was introduced primarily as a treatment for systemic hypertension and as an antiarrhythmic[1]. With respect to the practice of anaesthesia, the negative chronotropic effects of systemic propranolol have been used as an adjunct to controlled circulatory techniques, and to protect the heart from adrenergic stimulation associated with a variety of clinical conditions and situations. Similarly, the more recently introduced highly cardioselective, systemic beta adrenergic blocker, esmolol hydrochloride (Brevibloc, Anaquest Inc., Liberty Corner, NJ, USA) is utilized systemically to attenuate the cardiovascular response to laryngoscopy, to treat supraventricular tachycardias and as an adjunct to controlled circulatory techniques. In addition, esmolol has been found useful in the perioperative control of dysrhythmias and blood pressure[2].

Subsequent experience with the drug has produced evidence for the efficacy of esmolol as an anaesthetic adjunct. Geva et al. used esmolol as a substitute for fentanyl in 15 patients, as an adjunct of nitrous oxide/muscle relaxant technique. In this study, esmolol proved to be a useful replacement for fentanyl, resulting in stable haemodynamics, a low hormonal stress response, good recovery and no recall[3]. Concomitant studies in the rat showed that esmolol in a dose of 500 $\mu g\ kg^{-1}\ min^{-1}$ decreased halothane minimum alveolar concentration (MAC) by 10–15%[4]. More recently, Perel and Shneider found even greater reductions of the MAC for halothane in rats breathing nitrous oxide[5].

The aim of the present study was to assess the efficacy of esmolol as an anaesthetic adjunct in a homogeneous patient group with respect to type and duration of surgery, age or sex.

Methods

Forty women having an ASA physical status I or II and presenting for elective laparoscopic tubal fulguration were enrolled in the study. Patients with a history of hypertension or reactive airway disease were excluded. Of these 40 patients, 21 were classified as physical status II, 17 of these on the basis of smoking. Informed consent was obtained for the experimental protocol approved by our Institutional Review Board. Patients were assigned to either a fentanyl or an esmolol protocol via a computer-generated randomization sequence. All patients received 5% dextrose in 0.45% saline via an 18-gauge cannula in the left arm, and were monitored with an automatic sphygmomanometer, a three-lead electrocardiogram (EKG), pulse oximeter, precordial stethoscope, and a twitch monitor. Inspired/expired nitrous oxide and carbon dioxide were monitored by a

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mass spectrometer (Perkin-Elmer, Milwaukee, WI, USA). All patients received intravenous midazolam (0.02 mg kg^{-1}) prior to induction. Patients were induced with propofol, 2.5 mg kg^{-1}, ventilated with 70% nitrous oxide in oxygen, paralysed with vecuronium 0.1 mg kg^{-1}, intubated with a 7.0 mm endotracheal tube using a MacIntosh-3 blade upon disappearance of all neuromuscular activity. All endotracheal intubations were carried out on the first attempt. Following the securing of the endotracheal tube, an orogastic tube was passed, suctioned and left in place. Blood pressures were measured continuously following induction, every minute for 2 min following intubation and every 3 min subsequently. Inspired nitrous oxide levels were kept at 70%. Minute ventilation was adjusted to give end-tidal carbon dioxide levels of 22–25 mmHg. Muscle relaxation was maintained with intravenous vecuronium as monitored by the train of four.

Patients randomized to fentanyl received 2 μg kg^{-1} during induction. Subsequent fentanyl was given at the discretion of the anaesthesiologist either in anticipation of surgical stimulation or a perception of light anaesthesia as judged by increases of blood pressure and heart rate. Patients randomized to esmolol received a loading dose of 2 mg kg^{-1} during induction. Following intubation an esmolol infusion was started using an infusion pump (Bard MedSystems, North Reading, MA, USA). Initial infusion rates were set at approximately 300 μg kg^{-1} min^{-1} and adjusted in anticipation of increased surgical stimulation (e.g. abdominal trocar insertion), or in response to sudden increases in heart rate, blood pressure, or most importantly, pupillary dilation. Except for the pupillary response, the indications for adjustments of the anaesthetic were the same for both fentanyl and esmolol. Esmolol infusion or fentanyl administration were discontinued following abdominal decompression and removal of instruments from the cervix and abdomen. The abdominal wounds were infiltrated with 5 ml 0.25% bupivacaine for postoperative analgesia. Muscle relaxation was reversed with neostigmine 0.07 mg kg^{-1} and glycopyrrolate 0.015 mg kg^{-1} following return of the patient to the supine position together with a 1/4 train of four. Nitrous oxide was discontinued at the time of reversal of muscle relaxation. Times from reversal of the muscle relaxants to a return of cognitive function, such as eye opening or a hand squeeze upon command, together with the time from reversal of muscle relaxants to extubation, were noted. In addition, times between extubation and ambulation and patient discharge were recorded. Recovery room events were supervised and recorded by the same experienced recovery room nurses who were only told that the patients had received a balanced nitrous oxide relaxant technique. To be eligible for discharge the patients had to meet specified objective criteria which included: stable vital signs, presence of swallow, cough and gag reflexes, absence of respiratory distress, patient ambulatory, absence of dizziness, nausea, or vomiting, patient alert and oriented, patient successfully voided, and a postanaesthesia recovery score of 10[6,7]. All patients were questioned prior to discharge and at home the next day, regarding recall.

Data are expressed as means ± SEM. Results were analysed by a one-way analysis of variance followed by Student's paired t test. χ^2 tests were used for descriptive variables. A P value less than 0.05 was considered statistically significant.

Results

Two patients from the fentanyl group developed mild wheezing during the surgical procedure with increased peak airway pressures but no arterial oxygen desaturation. In these patients, isoflurane was added to the anaesthetic, the patients removed from the study, and their place in the randomization sequence repeated. No patients from the esmolol group were removed from the protocol. There were no differences between the two groups with respect to age, height, weight and duration of anaesthesia (induction to extubation), as shown in Table 1. In addition, blood pressure and heart rates showed no significant differences between the two groups at rest (basal), before or after induction, or before or after intubation (Table 2). Time of return of cognitive function and time from muscle relaxant reversal to extubation showed no difference between the two groups (Table 3). Upon admission to the recovery room, postanaesthetic recovery scale (PARS) scores were very similar. Furthermore, 13 of the esmolol group and 11 of the fentanyl group, were described as drowsy upon admission to the recovery room. Only one patient of either group received an analgesic for postoperative pain: this was a patient of the esmolol group who received 12.5 mg of demerol intravenously. Patients from the fentanyl group took significantly longer to become ambulatory and to be discharged as shown in Table 3. The delay in both ambulation and discharge achieved significance at a P value of <0.01. Factors related to the use of narcotics thought to contribute significantly to delayed ambulation and discharge, namely nausea and urinary retention, are shown in Table 4. Such adverse recovery room events were significantly higher in the fentanyl group at a P value of less than 0.05 using a χ^2 square test. No patient from either group had any evidence of intraoperative awareness either immediately postoperatively or on the following day.

Table 1. Patient demographic and intraoperative data for the treatment groups (means ± SEM)

	Esmolol	*Fentanyl*
Group size (*n*)	20	20
Age (yr)	31.3 ± 1.7	33.8 ± 1.6
Height (cm)	139.0 ± 1.4	141.9 ± 1.4
Weight (kg)	65.4 ± 3.1	66.2 ± 3.7
Total fentanyl (μg)	–	225.0 ± 9.6
Total esmolol (mg)	1623.0 ± 70.1	–
Anaesthetic duration (min)	67.9 ± 3.3	72.6 ± 3.5

Table 2. Peri-induction/intubation haemodynamics (means ± SEM)

	SBP (mmHg)		DBP (mmHg)		HR (bts min^{-1})	
	Esmolol	*Fentanyl*	*Esmolol*	*Fentanyl*	*Esmolol*	*Fentanyl*
Basal	108.9 ± 3.5	115.1 ± 2.1	70.8 ± 2.9	75.1 ± 2.0	73.8 ± 2.6	75.4 ± 2.5
Pre-induction	126.4 ± 3.8	127.3 ± 2.8	72.1 ± 2.4	74.2 ± 2.8	73.3 ± 2.8	73.5 ± 2.9
Post-induction	91.5 ± 2.4	89.1 ± 2.9	54.3 ± 1.8	48.8 ± 2.1	76.9 ± 1.9	71.3 ± 2.9
Pre-intubation	93.3 ± 2.5	89.8 ± 2.9	55.0 ± 1.8	49.2 ± 2.1	79.0 ± 1.7	70.9 ± 2.8
Post-intubation	129.4 ± 3.6	131.7 ± 5.5	82.9 ± 2.5	80.1 ± 4.3	82.9 ± 2.2	82.0 ± 3.2

SBP, Systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 3. Recovery times in minutes (means ± SEM)

Recovery times	*Esmolol*	*Fentanyl*
Reversal – cognitive response	2.3 ± 0.2	2.6 ± 0.2
Reversal – extubation	3.9 ± 0.2	4.2 ± 0.4
Extubation – ambulation	96.4 ± 6.4	133.4 ± 11.4*
Extubation – discharge	147.7 ± 7.4	190.6 ± 12.9*

*Significant at P value of <0.01.

Table 4. Recovery room events delaying discharge

	Esmolol	*Fentanyl*
Nausea and vomiting	1	5
Nausea only	3	4
Urinary retention	0	3
Total	4	12*

*Significant at P value <0.05.

Discussion

By confining this study to a single surgical procedure (laparoscopic tubal ligation) a high level of homogeneity was achieved with respect to the duration and degree of surgical stimulation together with morphology of the patient population studied. The patients in each group were equally divided between ASA physical status I and II. The high preponderance of smokers (42.5% overall) reflected current smoking trends.

The anaesthetic drugs for the control group, namely propofol, fentanyl, nitrous oxide and vecuronium, constituted a commonly used and appropriate anaesthetic technique for a laparoscopic tubal ligation carried out in an ambulatory surgery unit. We could not justify a control anaesthetic utilizing only the induction dose of propofol, nitrous oxide and muscle relaxant. Even with the use of midazolam for amnesia, the potential for awareness and significant cardiovascular instability in this young healthy population, was just too great. The long elimination half-life of fentanyl tends to result in significant cumulative effects when administered as a continuous infusion. Therefore, fentanyl is usually administered as repeated intravenous boluses and was so used in this study. In contrast, esmolol with an ultrashort elimination half-life, is invariably administered as a continuous infusion. Because of the differences in the most safe and effective methods of drug administration of the two groups in comparing fentanyl and esmolol as anaesthetic adjuncts, it was felt that a double-blind design would result in inappropriate fentanyl doses and less than optimal anaesthetic management. Recovery room care was provided by and assessments made by experienced recovery room nurses, who progressed the patients through the stages of recovery based on standard care patterns and discharge criteria as discussed above.

Any anaesthetic technique relying primarily upon nitrous oxide, modest hyperventilation, and a muscle relaxant has a high potential for intraoperative awareness[8]. Consequently, all patients were given the short-acting amnestic midazolam prior to induction (0.02 mg kg^{-1}). The high percentage of each patient group exhibiting observable sedation upon admission to the recovery room accounted for PARS scores of 8.9 ± 0.2 for the fentanyl group and 9.1 ± 0.2 for the esmolol group. With respect to the fentanyl group, such sedation was compatible with the cumulative residual sedation from midazolam, propofol and fentanyl. As there was no observable difference in sedation between the two groups, it was our impression that intravenous esmolol in the doses used (approximately 0.35 mg kg^{-1} min^{-1}) resulted in significant postoperative sedation.

On average, the fentanyl group took significantly longer to ambulate and to be discharged from the recovery room. The greater incidence of nausea (vomiting) and urinary retention appeared to be the major reason for this difference: the effects of narcotics upon postoperative nausea being well documented[9] particularly when used as part of a balanced technique.

This study is consistent with previous observations that a continuous infusion of esmolol can reduce anaesthetic requirements in animals[4,5]. The interaction of drugs and/or ancillary anaesthetic techniques to produce a desirable therapeutic effect is a cornerstone

of modern anaesthetic practice. Such interactions ideally maximize desired effects and reduce pharmacological side effects of the drugs involved. Reductions of anaesthetic requirements have been attributed to hypocarbia secondary to hyperventilation[15], skeletal muscle paralysis[11] and autonomic drugs such as α-2 agonists. For example, the α-agonist, clonidine has been reported to reduce fentanyl requirement[12,13], and to enhance the effects of inhalational agents[14]. In the current study, moderate hyperventilation, skeletal muscle paralysis and esmolol had the potential to affect anaesthetic requirements.

Hyperventilation producing hypocapnia may affect anaesthetic requirements by a variety of possible mechanisms[15] including: the modification of alveolar anaesthetic concentrations of any concomitant inhalational agent; the inhibition of neural activity between the respiratory centres and the accessory muscles of respiration, particularly the abdominal muscles; and the production of cerebral vasoconstriction which may result in relative ischaemia of the cerebral cortex having a direct effect on the reticular activating system, the so-called forebrain deafferentation[10].

With respect to muscle relaxation, Forbes et al.[11], reported that pancuronium decreased the MAC of halothane by 25% in surgical patients. A direct effect on the central nervous system or a deafferentation of the central nervous system via an effect of pancuronium upon the muscle spindles, was put forward to explain the above interaction. A disinhibition of the accessory muscles of respiration due to the hypocarbia as discussed above could also contribute to this deafferentation. A subsequent study failed to confirm an effect of skeletal muscle relaxation upon anaesthetic potency[16].

There is currently little information concerning the site of action of esmolol as an anaesthetic adjunct. Partridge and Kon[4] postulated that if esmolol mediates its anaesthetic effect indirectly, it may do so by reducing circulating catecholamines. However, in the study of Geva et al.[3], plasma catecholamine levels were no different in the esmolol/nitrous oxide group, compared to the fentanyl/nitrous oxide group. Any sympatholytic drug has the potential to effect a hypnotic action via hypnogenic mechanisms postulated as the basis for active sleep. For example, Steriade and McCarley discuss two likely cerebral hypnogenic structures: the medullary solitary tract nucleus and the preoptic area of the basal forebrain, together with a wide variety of aminergic neurons utilizing norepinephrine, epinephrine and serotonin as neurotransmitters[17]. These neurons inhibit rapid eye movement (REM) and are located primarily in the locus coeruleus, dorsal raphe and the peribrachial region. It is of particular interest that the locus coeruleus, as a principal site of REM inhibitory aminergic neurons, is also a site of action of α-2 agonists together with a separate opiate enhancement mechanism[18].

A further possible mechanism of action of esmolol is by inhibition of the sympathomimetic actions of nitrous oxide. The increased sympathetic activity during nitrous oxide anaesthesia[19] has been found to antagonize both the central nervous system depression by isoflurane[20] and the isoflurane induced suppression of learning[21]. The primary anaesthetic in the current study is 70% nitrous oxide. Any potentiation of the potency of the nitrous oxide by the sympatholytic effects of esmolol could explain the efficacy of esmolol as a substitute for fentanyl in the technique under study.

In conclusion, in 40 patients undergoing laparoscopy for bilateral tubal ligation, anaesthetized with a nitrous oxide/muscle relaxant technique with modest hyperventilation, esmolol proved to be the equal of fentanyl in terms of peri-induction and intubation haemodynamics, operative conditions and restitution of cognitive function and independent respiration. Patients receiving esmolol had a lower incidence of nausea and urinary retention, were able to walk earlier and were discharged sooner than those who received fentanyl.

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References

1 Black JW, Stephenson JS. Pharmacology of a new beta-adrenergic receptor blocking compound. *Lancet* 1962; **2**: 311–14
2 Kaplan J. Role of ultrashort acting beta blockers in the perioperative period. *J Cardiovasc Anesth* 1988; **2**: 683–9
3 Geva D, Sagi D, Perel A. Esmolol/nitrous oxide/relaxant – a new effective anesthetic maintenance technique. (abstr) *Anesthesiology* 1990; **73**: A320
4 Partridge BL, Kon DF. Esmolol reduces halothane MAC in rats. (abstr) *Anesthesiology* 1990; **73**: A333
5 Perel A, Shneider A. Esmolol reduces MAC of halothane in the presence of N_2O in rats. (abstr) *Anesthesiology* 1993; **79**: A421
6 Kitz DS, Robinson DM, Schiavone PA, Walsh PR, Conahan TJ. Discharging outpatients. *AORN Journal* 1988; **48**: 87–91
7 Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970; **40**: 924–34
8 Waters DJ. Factors causing awareness during surgery. *Br J Anaesth* 1968; **40**: 259–64
9 Janhunen L, Tammisto T. Postoperative vomiting after different modes of general anesthesia. *Ann Chir Gynaecol* 1972; **61**: 152–9
10 Geddes IC, Gray TC. Hyperventilation for the maintenance of anesthesia. *Lancet* 1959; **2**: 4–6
11 Forbes AR, Cohen NH, Eger EI. Pancuronium reduces halothane requirement in man. *Anesth Analg* 1979; **58**: 497–9
12 Horvath G, Benedek G, Szikszay M. Enhancement of fentanyl analgesia by clonidine plus verapamil in rats. *Anesth Analg* 1990; **70**: 284–8
13 Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 35–42
14 Bloor BC, Flacke WE. Reduction in halothane

anesthetic requirement by clonidine on alpha-adrenergic agonist. *Anesth Analg* 1982; **61**: 741–5

15 Cullen DJ, Eger EI. The effect of extreme hypocapnia on the anesthetic requirement (MAC) of dogs. *Br J Anaesth* 1971; **43**: 339–43

16 Fahey MR, Sessler DI, Cannon JE, Brady K, Stoen R, Miller RD. Atracurium vecuronium, and pancuronium do not alter the minimum alveolar concentration of halothane in humans. *Anesthesiology* 1989; **71**: 53–63

17 Steriade M, McCarley RW (eds). *Brainstem Control of Wakefulness and Sleep*. New York: Plenum Press, 1990

18 Aghajanian GK, Wang YY. Common α-$_2$ – and opiate effector mechanisms in the locus coeruleus: Intracellular studies in brain slices. *Neuropharmacol* 1987; **26**: 793–9

19 Smith NT, Eger EI, Stoelting RK, Whayne TF, Cullen D, Kadis LB. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. *Anesthesiology* 1970; **32**: 410–21

20 Yhi-Hankala A, Lindgren L, Porkkola T, Jantti V. Nitrous oxide medicated activation of the EEG during isoflurane anaesthesia in patients. *Br J Anaesth* 1993; **70**: 54–7

21 Chortkoff BS, Bennett HL, Eger EI. Does nitrous oxide antagonize isoflurane-induced suppression of learning. *Anesthesiology* 1993; **79**: 724–32