Role of β-blockade in anaesthesia and postoperative pain management after hysterectomy

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Background. Perioperative use of β-blockers has been advocated as a strategy to prevent cardiac sequelae. This study evaluated the influence of perioperative esmolol administration upon anaesthesia and postoperative pain management amongst patients undergoing hysterectomy.

Methods. Ninety-seven ASA I–II patients, undergoing abdominal total hysterectomy, were randomly divided into one of two groups. Patients in the Esmolol group received an i.v. loading dose of esmolol 0.5 mg kg⁻¹ followed by infusion of 0.05 mg kg⁻¹ min⁻¹ before anaesthesia induction. The infusion was documented at the completion of surgery. The Control group received a volume of normal saline. After surgery, all patients were treated with patient-controlled i.v. analgesia (PCA), which was programmed to deliver 1 mg of morphine on demand for 3 consecutive days. Pain intensity on movement and at rest, sedation score, and side effects were recorded.

Results. The two groups were comparable with respect to their characteristics. Patients in the esmolol group received significantly lower end-tidal isoflurane concentrations (1.0 (0.3) vs 1.4 (0.5)% respectively; P<0.001) and fentanyl (0.9 (0.2) vs 1.2 (0.5) μg kg⁻¹, respectively; P=0.006) during anaesthesia. They also showed a reduced heart rate and arterial pressure response to tracheal intubation, skin incision, and tracheal extubation. The Esmolol group consumed less PCA morphine in 3 days (37.3 (8.4) vs 54.7 (11.2) mg, respectively; P=0.005). Pain intensity on movement and at rest, sedation score, and side effects were similar in the two groups.

Conclusion. The results suggest that perioperative esmolol administration during anaesthesia reduces the intraoperative use of inhalation anaesthetic and fentanyl, decreases haemodynamic responses, and reduced morphine consumption for the first 3 postoperative days.

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Monoaminergic receptors modulate the response to a painful stimulation. Among noradrenergic receptors, α-receptors appear to attract more attention than β-receptors with regard to pain modulation and analgesic efficiency. Previous studies have shown that continuous esmolol infusion decreased the plasma propofol minimal alveolar anaesthetic concentration (MAC) during propofol/nitrous oxide/morphine anaesthesia, and reduced isoflurane MAC during isoflurane/alfentanil anaesthesia. In animals the β-antagonist propranolol significantly prolonged sodium channel blocker (Tetrodotoxin)-induced sciatic nerve blockade. Clinical investigations have demonstrated significantly more rapid recovery and reduced postoperative analgesic requirements and the improvement of intraoperative haemodynamics in those patients receiving metoprolol. Also, β-antagonists have been effectively used for the management of post-traumatic stress disorder (PTSD), the symptoms of which are similar to, and were suggested to result from, the psychiatric sequelae of some degree of intraoperative awareness.

Therefore, we hypothesize that perioperative β-antagonist administration may be beneficial in reducing the stress responses induced by surgery, and also improve postoperative outcome.

Esmolol is an ultra short-acting, cardio-selective β₁-receptor antagonist that is effective in blunting adrenergic responses to several perioperative stimuli, including the application of a laryngoscope associated with tracheal intubation, intraoperative events, and tracheal extubation. Its use has been promoted to minimize the deleterious effects of intraoperative hypertension and tachycardia upon
myocardial oxygen consumption. Esmolol is a short potent β-receptor antagonist (β1-selectivity), and unlike propranolol, is associated with little sedative effect, no analgesic activity, and no local anaesthetic properties.

Hence, we have conducted a prospective, randomized, double-blind trial to evaluate the influence of perioperative esmolol and placebo upon anaesthesia and postoperative pain.

**Methods**

**Patients**

Approval by the Human Investigation Committee and written, informed consent from each patient were obtained. ASA physical status I–II patients, undergoing abdominal total hysterectomy, were enrolled in this study. Patients were selected randomly, using a table of random digits, and equally divided into one of two groups (Esmolol vs Control). Patients with a history of ischaemic heart disease, heart block, pulmonary, hepatic or renal disease, or were allergic history to opioids, were excluded from the study. Patients who took the analgesics (such as NSAID, opioids, or paracetamol) regularly or 3 days before the operation were also excluded. A total of 100 patients were enrolled into the study programme initially, although two patients from the Esmolol group and one from the Control group were excluded because of failure to complete the entire study.

**Anaesthesia**

Before surgery, patients were instructed regarding the use of the visual analogue scale (VAS; 0=no pain, 10=worst possible pain), and the patient-controlled i.v. analgesia (PCA) device. Thirty minutes before the induction of anaesthesia, patients in the Esmolol group received a loading dose of esmolol (0.5 mg kg⁻¹ in 30 ml normal saline) over a period of 5 min followed by an i.v. infusion of esmolol (0.05 mg kg⁻¹ min⁻¹) until the closure of incision, whilst patients from the control group received the same volume of normal saline for loading and continuous infusion.

General anaesthesia was then induced in all patients with fentanyl (3 μg kg⁻¹), thiopental (5 mg kg⁻¹), and succinylcholine (2 mg kg⁻¹). Tracheal intubation was performed and atracurium (0.5 mg kg⁻¹ h⁻¹) administered in order to maintain an acceptable level of muscle relaxation during surgery. Isoflurane at an age-adjusted end-tidal concentration of 1.0–1.5 MAC in an air/oxygen mixture was administered in order to maintain anaesthesia. The relative depth of anaesthesia was then assessed, and the following autonomic responses were considered to be indicative of an inadequate depth of anaesthesia: (i) an increase in mean arterial pressure (MAP) more than 20% above baseline for more than 1 min; (ii) an increase in heart rate (HR) more than 20% above baseline for more than 1 min; (iii) somatic signs (e.g. purposeful movement, swallowing or grimacing); (iv) autonomic signs (e.g. lacrimation, mydriasis, facial flushing, or diaphoresis).

At the presence of such signs, the end-tidal isoflurane concentration or the dosage of fentanyl was titrated to increase the depth of anaesthesia. A Datex gas analyser calibrated immediately before anaesthesia was used to monitor airway gas concentrations continuously.

Surgery was commenced subsequent to stable end-tidal isoflurane concentrations having been maintained for a period of at least 10 min. Following skin incision, patients were observed for a response to the incision. When a patient's HR or MAP fluctuated to a level greater than 20% from the baseline value immediately before anaesthesia having been achieved, the end-tidal isoflurane concentration was titrated by 0.2% until such time that the haemodynamic profiles had returned to the preoperative baseline.

At the completion of surgery, patients in the Esmolol group had their esmolol infusion discontinued. An anaesthetist, who was not involved in any way with postoperative patient evaluation and who had had no prior patient contact, conducted the entire course of anaesthesia. Intraoperative hypotension and bradycardia was defined as, respectively, an MAP value less than 50 mm Hg and a HR lower than 40 beats min⁻¹. Those patients experiencing hypotension or bradycardia were treated with intermittent ephedrine (5 mg) or atropine (0.5 mg).

Double blinding was achieved by requesting our hospital pharmacy to prepare the infusion solution for subjects individually and label them with a particular subject’s identification number only. The specific code indicating to which group the subject had been assigned was retained by the pharmacy until the time of the study's conclusion. For reasons of patient safety, a sealed opaque envelope containing the randomized treatment assignment was kept with the patient in the operating room and post-anaesthesia recovery care unit.

**Postoperative management and evaluations**

After surgery, all patients received a PCA system (Abbott Pain Management Provider, IL, USA), which provided i.v. morphine (1 mg bolus) for postoperative analgesia upon patient demand with a 4-h limit of 20 mg morphine. The lockout time was 5 min. Pain intensity was evaluated using a visual analogue scale for movement (VASM), and whilst at rest (VASR) on a daily basis for 3 days subsequent to the completion of surgery. An anaesthetist in our Acute Pain Service assessed pain intensity and morphine usage at 08.00–10.00 on the first 3 days after the operation. A pain score of less than or equal to 3 was considered to represent satisfactory pain relief. Any patient who vomited more than three times in a day after surgery was treated with dexamethasone (5 mg) intravenously upon patient demand. The sedation level was recorded according to a four-point scale (0=awake and alert, 1=mildly sedated, easily aroused, 2=moderately sedated, but can be aroused by shaking, 3=deeply sedated, difficult to arouse, even by shaking).
Morphine consumption (mg) at the indicated time intervals and the associated side effects, such as nausea, emesis, pruritus, and respiratory depression were also recorded. Respiratory depression was defined as a ventilatory frequency of less than 8 b.p.m.. Each patient was asked to grade satisfaction (yes/no) at the end of PCA use. Both patients and observers were blinded with respect to treatment groups.

**Statistical analysis**

All data are presented as mean (SD). Patient characteristics and the cumulative morphine consumptions were analysed using one-way analysis of variance (ANOVA) with Post-hoc Bonferroni’s adjustment. Classification of operations, the incidence of side effects, and patient satisfaction were analysed using the χ² test or Fisher’s exact test as appropriate. Pain scores and sedation scores were analysed using the Mann–Whitney U-test. A value of $P<0.05$ was considered to represent statistical significance. Based upon our preliminary data, a priori power analysis indicated that 45 patients in each group would be a sufficiently large sample size to be adequate to detect a 20% reduction in morphine requirements on the first postoperative day, with a type-I error of 0.05 and a power of approximately 90%.

**Results**

Patient characteristics and quantity of esmolol used, total blood loss, and surgical duration for the two groups are shown in Table 1. There was no significant difference. Details of anaesthesia are also shown in Table 1. The concentration of isoflurane and intraoperative fentanyl used for anaesthesia maintenance in the Esmolol group was significantly lower than in the Control group ($P<0.05$). Intraoperative use of ephedrine and atropine was similar. HR during anaesthesia is indicated in Figure 1. The Esmolol group showed lower overall HR than the Control group, and HR during tracheal intubation, skin incision, and tracheal

| Table 1 | Patients and surgical characteristics included in the study (n=97). Values are mean (range), mean (std) or number. The two groups were similar for all values tested; only maintained isoflurane concentration and fentanyl used showed significant differences |
|------------------|------------------|------------------|
|                  | Esmolol group    | Control group    | $P$-value |
| Number           | 49               | 48               | 0.263     |
| Age (yr) (range) | 48.5 (30–79)     | 49.8 (27–75)     | 0.436     |
| Weight (kg)      | 57.4 (7.2)       | 61.3 (10.6)      | 0.591     |
| Height (cm)      | 153.6 (5.4)      | 155.6 (4.4)      | 0.481     |
| ASA (I/II)       | 21/28            | 24/24            | 0.917     |
| Total esmolol (mg) | 375.4 (143.2)   | –                | 0.835     |
| Total blood loss (ml) | 421 (375)     | 325 (308)        | <0.001    |
| Duration of surgery (min) | 122 (54)       | 138 (50)         | 0.006     |
| Maintained isoflurane (%) | 1.0 (0.3)   | 1.4 (0.5)        | 1.000     |
| Fentanyl used (µg kg⁻¹) | 0.9 (0.2)   | 1.2 (0.5)        | 0.495     |
| Number of patients needed ephedrine | 1 | 0 | 1.000 |
| Number of patients needed atropine | 2 | 0 | 0.495 |

![Fig 1](https://academic.oup.com/bja/article-abstract/93/6/799/266616)

**Fig 1** HR (beats min⁻¹): *$P<0.05$, significant inter-group differences; $^\#P<0.05$, significant intra-group differences compared with baseline.
extubation fluctuated less in the Esmolol group. The MAP variation during anaesthesia is depicted in Figure 2. There was no significant difference between the two groups with regard to MAP during anaesthesia, apart from the observation that a more severe arterial pressure response during tracheal intubation and skin incision occurred in the Control group ($P < 0.05$).

Pain intensity at rest (VASR) and upon movement (VASM) at various time points appeared to be similar between the groups (Figures 3 and 4). All patients were fully awake (sedation scores were zero after surgery when visited by our study team). Patients in the Control group used a greater quantity of PCA morphine than those from the Esmolol group at all times in the study (Figure 5). The mean total patient morphine consumption for the Control and Esmolol groups for the 3 postoperative days was 54.7 (11.2) and 37.3 (8.4) mg, respectively, $P=0.005$. The occurrence of side effects, such as nausea, vomiting, pruritus, and dizziness are shown in Table 2: there was no difference.

**Discussion**

Many previous studies have focused on the relationship between perioperative β-block use and the occurrence of various cardiac events. However, to the best of our knowledge, very few, if any, have addressed the impact of the use of a β-block upon anaesthesia and postoperative pain management. In 1982, Stanley and colleagues demonstrated reduced sufentanil requirements for unconsciousness before coronary-artery bypass surgery in
patients receiving chronic propranolol treatment. Some studies have also suggested that β-antagonist use reduced anaesthetic requirements during anaesthesia, reduced inhalation anaesthetic MAC, and improved postoperative recovery. In 2001, Coloma and colleagues even suggested that perioperative β-antagonist administration was an alternative to remifentanil in maintaining intraoperative stable haemodynamics. However, the specific mechanism by which β-block potentiates the analgesic effect of an opioid or an inhalation anaesthetic remains controversial. For example, in 1982, Yaksh and colleagues reported that the spinal β-adrenoceptors were probably not involved in pain modulation at the spinal cord level, as the intrathecal administration of isoproterenol did not appear to alter the nociceptive threshold as measured in the hot plate, the tail flick, and the writhing tests for rats. In addition, Hageluken and colleagues demonstrated that β-adrenergic antagonists activate G-proteins in isolated cell membranes, and it was suggested also that this property resembles the mechanism of central analgesia as induced by clonidine. Inhibitory G protein-coupled receptor agonists act upon post-synaptic inhibition via G protein-coupled potassium channels or via the pre-synaptic inhibition of neurotransmitter release.

**Fig 4** VASM pain intensity on movement (mean and SD). No significant differences.

**Fig 5** Morphine consumption (mg). *P<0.05.

**Table 2** Main side effects recorded for patients receiving esmolol (n=49) or placebo (n=48) during day 1 and day 2 after surgery. Values are shown as numbers (%). There was no case experiencing nausea, vomiting, pruritus, or dizziness in postoperative day 3. The two groups were similar for all values tested.

<table>
<thead>
<tr>
<th></th>
<th>Esmolol group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (20.0)</td>
<td>12 (25.0)</td>
<td>0.589</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (8.0)</td>
<td>4 (12.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (8.0)</td>
<td>4 (12.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (12.2)</td>
<td>4 (12.6)</td>
<td>0.740</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8.0)</td>
<td>4 (8.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (8.0)</td>
<td>0 (0)</td>
<td>0.117</td>
</tr>
</tbody>
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through the regulation of voltage-gated Ca\textsuperscript{2+} channels; such a pathway underlies the antinociceptive effect of clonidine.\textsuperscript{22}

Propranolol administration has been shown to decrease its own metabolism, as also that of certain other drugs, by eliciting a reduction in hepatic blood flow.\textsuperscript{23} This could affect the metabolism of drugs with a large hepatic extraction ratio, such as fentanyl, and it would seem likely that propranolol use would result in the prolongation of the analgesic effect of fentanyl and also elicit a reduction in postoperative opioid consumption. Although the effect of esmolol upon drug metabolism has not yet been thoroughly investigated, the elimination of esmolol subsequent to its administration appears to be independent of renal or hepatic function as it is metabolized by red blood cell cytosol esterase to an acid metabolite and methanol.\textsuperscript{24} Thus, it seems unlikely that the infusion of esmolol would alter the pharmacokinetics of opioids.

The fact that esmolol attenuated the cardiovascular response to laryngoscope application and tracheal intubation when used in bolus or continuous infusion\textsuperscript{10,11,25,26} is confirmed by our results. In 2002, Auerbach and colleagues suggested that perioperative stimulation such as laryngoscope application, tracheal intubation, skin incision, and/or tracheal extubation might induce hypertension and tachycardia, increasing the risk of myocardial events. These authors suggested that a $\beta$-antagonist should be given perioperatively only in high-risk cardiac patients.\textsuperscript{27} In our study, the fact that no patient, from either group, experienced any cardiac events during anaesthesia or during the postoperative period might be attributable to the relatively young and healthy status of our patients.

In 1999, Zaugg and colleagues demonstrated that intraoperative atenolol administration reduced postoperative morphine consumption as well as providing a more rapid recovery from anaesthesia. However, it did not reduce the plasma concentrations of stress hormones such as neuropeptide Y, norepinephrine, epinephrine, or cortisol.\textsuperscript{6} However, atenolol is a $\beta$-antagonist with a half-life of 6–9 h, which is substantially longer than that of esmolol.\textsuperscript{28} Therefore, atenolol might exert significant influence upon various physiological systems even several hours after its administration. Further, their study included many different types of surgery.

Zaugg and colleagues found that the administration of a $\beta$-antagonist appeared to exert no influence upon pro-inflammatory or inflammatory interleukin profiles.\textsuperscript{29} Such a result was interpreted to imply that the beneficial impact of a $\beta$-antagonist upon anaesthesia and postoperative pain management is not necessarily attributable to the influence suppression effect of stress hormone or pro-inflammatory cytokines.

There are some similarities between postoperative pain and PTSD. One of the aetiologies of PTSD is acute stress reaction, which leads to chronically increasing secretions of epinephrine and norepinephrine and higher baseline HR and arterial pressure.\textsuperscript{30,31} The symptoms similar to those of acute postoperative pain. Anti-adrenergic agents are one choice of pharmacological treatment of PTSD reducing adrenergic dysregulation and subsequent sequelae. Several case reports and open trials have found positive effects of propranolol or clonidine on PTSD symptoms, although the mechanism has to be investigated further.\textsuperscript{32} We found that intraoperative use of esmolol attenuated intraoperative nociceptive stimulation responses and reduced postoperative morphine consumption.

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