Anaesthesia, 2002, **57**, pages 1195–1212

FORUM

Facial fractures and submental tracheal intubation

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Summary

Submental tracheal intubation is a simple, quick and effective alternative to oral and nasal tracheal intubation or tracheostomy in the surgical management of selected patients with craniomaxillofacial injuries. It has a low morbidity and it does not impede the surgical field, allowing for temporary maxillo-mandibular fixation (jaw wiring) intra-operatively, and nasal assessment, manipulation and bone grafting, either simultaneously or as an independent procedure. We report 12 cases utilizing this technique in this retrospective study, this includes 11 patients with midfacial fractures and associated base of skull fractures, and one patient who underwent an elective Le Fort III advancement. The techniques and indications for submental tracheal intubation are described.

Keywords *Anaesthesia*: equipment; tubes tracheal. *Intubation tracheal*: submental; complications.

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Accepted: 6 February 2002

There are specific problems associated with airway management in patients with midface or panfacial fractures and possible base of skull fractures. Nasal tracheal intubation in these patients is controversial, particularly if performed without the benefits of a fibreoptic bronchoscope, because of the potential complications, including cranial intubation, epistaxis and intracranial or sinonasal infection [1–4]. Furthermore, comminuted midface or naso-orbito-ethmoidal complex fractures may cause a physical obstruction to the passage of a nasal tube and the tube may interfere with the assessment and reduction of these fractures [5]. It is often necessary during the reduction of facial fractures to establish dental occlusion and perform temporary maxillo-mandibular fixation (jaw wiring) intra-operatively. This precludes the use of an oral tube at this point in the procedure and may therefore necessitate a tube change.

Tracheostomy is still considered the treatment of choice for patients with extensive craniomaxillofacial injuries and multisystem trauma and those who require long-term ventilatory support. However, it is associated with significant morbidity and complications such as haemorrhage, surgical emphysema, tube blockage, recurrent laryngeal nerve injury, tracheal stenosis and poor scar appearance [6].

An alternative method of establishing an airway in patients who require maxillofacial surgery but who do not require long-term ventilatory support is to perform submental tracheal intubation, the technique being originally described by Hernández Altemir in 1986 [7]. This provides a secure airway and allows unimpeded surgical access to the oral cavity and midface, whilst avoiding the potential complications associated with nasal intubation and tracheostomy.

Methods

To perform this technique, the patient's trachea is intubated orally using an armoured tracheal tube. Prior to this the universal connector must be removed or cut off and replaced with a removable connector to allow easy detachment. Patients who are already intubated must have

their tracheal tube replaced with a re-inforced tube under direct laryngoscopy or by using a lubricated tube exchanger. Using an aseptic technique, the skin of the neck, lower face and the end of the tracheal tube are cleaned with an appropriate antiseptic solution. Care must be taken not to dislodge the tube at this stage. A 1.5-cm skin crease incision is made in the submental region, just medial to the lower border of the mandible, approximately one third of the way from the symphysis to the angle of the mandible.

The side of the mandible that is used may be dictated by the presence of a concurrent mandibular fracture. Mouth opening is maintained using a gag or dental prop and the tongue is retracted, exposing the floor of the mouth. A closed pair of medium-sized artery forceps are then introduced into the submental incision and blunt dissection is carried out towards the floor of the mouth, staying as close as possible to the inner (lingual) aspect of the mandible to avoid damaging the sublingual gland, submandibular duct and lingual nerve. The tissue layers encountered are subcutaneous fat, platysma, investing layer of deep cervical fascia and mylohyoid muscle until the tip of the artery forceps tents the mucosa of the floor of the mouth, at the junction of the attached lingual mucosa. The tented oral mucosa is then incised allowing easy delivery of the tip of the artery forceps into the oral cavity. The blades of the forceps are then separated to a distance equating the diameter of the tube and gently passed in an oral-to-skin direction to reduce any soft tissue resistance for subsequent passage of the tube. The patient's lungs are then ventilated with 100% oxygen for several minutes and the tracheal tube briefly disconnected from the breathing circuit. The universal connector is removed and the pilot tube cuff (deflated) is grasped by the artery forceps and pulled through the passage in the floor of the mouth. The tip of the artery forceps are then quickly re-inserted through the submental incision to grasp the end of the tracheal tube, which is also pulled through in a similar way.

The connector is then re-attached, the cuff re-inflated and the tracheal tube reconnected to the breathing circuit. The tracheal tube then lies in the sulcus in the floor of the mouth between the tongue and the mandible. The position of the tracheal tube is checked using capnography and chest auscultation and a careful note made of the distance marking on the tube at the skin exit site.

The tube is then secured to the skin of the submental region with adhesive tape circumferentially applied to the tube and a heavy (2/0) black silk suture.

The elastoplast in addition prevents accidental inward displacement of the tube during manipulation of the mandible. A throat pack can then be inserted if required.

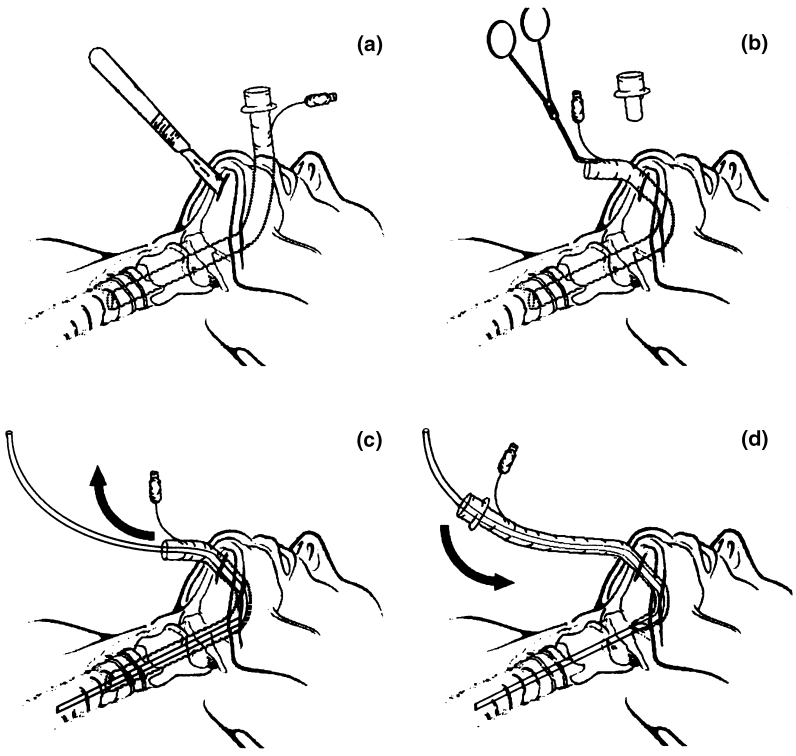

Figure 1 Schematic diagram showing submental intubation procedure using a tube exchanger. (a) Submental incision. (b) Free end of orotracheal tube is pulled through submental incision after removal of the connector. (c) After insertion of the tube exchanger, the damaged tube is pulled out. (d) Replacement with a new re-inforced tracheal tube. Reproduced with permission from: Drolet P, Girard M, Poirier J, Grenier Y. Facilitating submental tracheal intubation with an tracheal tube exchanger. Anesthesia & Analgesia 2000; 90: 222–3.

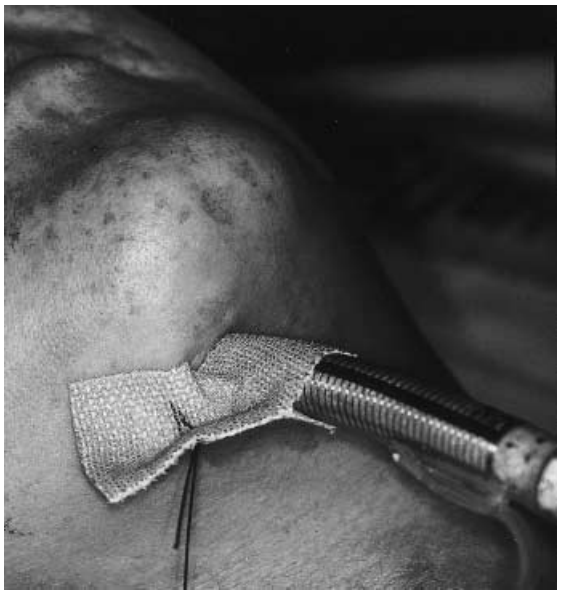

Figure 2 Photograph showing the tracheal tube secured to the submental region with adhesive tape and sutures.

At the end of the operation the procedure is reversed. The skin sutures are cut and the tracheal tube is briefly disconnected from the breathing circuit. The universal connector is then removed and the deflated pilot cuff is pulled back through the passage in the floor of the mouth, followed by the tracheal tube. The connection is then re-established and the tube is secured. The submental incision is closed using three or four monofilament skin sutures that are removed after 5–7 days. No attempt is made to close the oral defect. All 12 patients in our series received peri-operative broad-spectrum antibiotics and postoperative 0.12% chlorhexidine mouth washes.

Results

Between January 1999 to the present we have performed 12 submental intubation procedures on eight male and four female patients age 6–53 years (mean 28 years). Ten patients had midfacial fractures at the Le Fort II/III level with associated anterior base of skull fractures, of which five patients in addition had naso-ethmoidal fractures and one patient had an associated mandibular fracture. One patient had an isolated mandibular fracture associated with a base of skull fracture and one patient underwent an elective Le Fort III advancement osteotomy. All the patients had reversal of the submental tracheal tube at the end of the operation and nine patients were extubated in theatre. Three patients had delayed oral extubation in the Intensive Care Unit between 1 and 3 days postoperatively.

Minor complications were encountered in three patients during the submental tracheal intubation procedure. In the first patient where the technique was used, the tube was accidentally dislodged into the right main bronchus during manipulation of the mandible, as it had not been adequately secured to the skin of the submental region. Venous bleeding was encountered in one patient when the pilot tube cuff was pulled back into the mouth, and accidental partial extubation occurred in a paediatric case when the tracheal tube was being pulled through the submental incision.

Discussion

The submental route for tracheal intubation was first described by Hernández Altemir in 1986 [7]. This technique provides a secure airway whilst at the same time allowing an unobstructed surgical field for adequate reduction and fixation of midface and panfacial fractures. Submental tracheal intubation also avoids the potential complications associated with nasal intubation and tracheostomy and obviates the need for a tube change during the operation. In addition to panfacial trauma where temporary intermaxillary fixation (jaw wiring) is required intra-operatively, submental tracheal intubation may also be indicated in patients undergoing simultaneous elective mandibular orthognathic surgery and rhinoplasty procedures, and in cleft lip and palate patients undergoing orthognathic surgery where nasal obstruction may preclude the use of a nasal tube. Stoll [8] described a similar technique to submental intubation but where the incision is placed further posteriorly in the submandibular region and Prochno [9] reported 14 patients who underwent submandibular transmylohyoid intubation. The submental route as described by Hernández Altemir has subsequently been modified by Green & Moore [10] who described using two tracheal tubes. The patient is initially intubated in the normal fashion with an orotracheal tube. A submental incision is then made and a second tube pulled through the incision, cuff end first and passed into the trachea after removal of the first tube. This was considered safer than a single tube, which may be dislodged as it is pulled through the submental incision or if difficulties were encountered re-attaching the connector. MacInnis & Baig reported 15 patients in which the submental incision was modified to utilise a strict midline approach, because of difficulties they encountered with tube passage, bleeding and sublingual gland involvement using a lateral incision [11].

Drolet [12] reported using a lubricated tube exchanger (Cook), passed through the tracheal tube once it has been pulled through the submental incision, and the tube then

exchanged for a fresh re-inforced one. This ensures that a ventilation device remains in the airway at all times and avoids the problem of fixed connectors to re-inforced tracheal tubes.

We have found that some armoured tubes are not suitable for use with submental tracheal intubation, as their connectors are not designed to be removed. The end of the tube often has to be cut off and when re-attached may form a loose connection or require cut edges of re-inforcing wire to be trimmed. This may take a few minutes at a time when the patient is apnoeic and therefore requires pre-oxygenation with 100% oxygen for several minutes prior to removing the end of the tube. More recently in two patients in this series we have used a 100% silicone wire-reinforced tube (Euromedical ILM Endotracheal Tube – Intravent Orthofix) designed for use with the intubating laryngeal mask airway (ILMA).

This tube has the advantage of having a connector that is specifically designed for detachment and re-attachment during insertion of the ILMA, making it ideal for submental tracheal intubation. Hernández Altemir has also recently reported on the use of the laryngeal mask airway via the submental route [13]. The morbidity associated with submental tracheal intubation appears to be low [14–17]. Potential complications include infection, damage to adjacent structures such as the submandibular and sublingual glands, sublingual duct and lingual nerve, oro-cutaneous fistula and scar formation.

In our series there were three minor complications. Neck flexion and manipulation of the mandible, in one patient, resulted in the tube gradually being pushed down into the right main bronchus as it had not been secured properly to the skin. Following this we secured the tubes in place using circumferential adhesive tape and skin sutures. Venous bleeding was encountered in one patient when the pilot tube cuff was pulled back into the mouth, which responded to simple pressure for a few minutes with gauze packs. Partial extubation occurred in a 6-year-old patient as the tracheal tube was being pulled through the submental incision. This was detected immediately by the anaesthetist who repositioned the tracheal tube under direct laryngoscopy. No other complications were encountered in the intra-operative or postoperative period and the appearance of the submental scar has been acceptable in all patients (mean follow-up 13 months).

Caron [18] reviewed 25 patients who underwent submental intubation and found only one complication – that of a superficial wound infection. Stranc [19] reported a case of an 29-year-old man that developed a submandibular mucocoele 6 months following submandibular intubation for panfacial fractures. This was performed according to the technique described by Stoll, with two modifications; blunt intra-oral mucosal perforation and dissection from the mouth to the skin to create a passage and the use of a second tracheal tube which is pulled through the incision into the mouth for subsequent tracheal tube exchange. The authors felt this complication could have been avoided by incising the oral mucosa prior to blunt dissection.

In our series, all patients were converted back to oral tracheal tubes at the end of the operation and most patients were extubated in theatre. Three patients had delayed oral extubation in the intensive care unit because

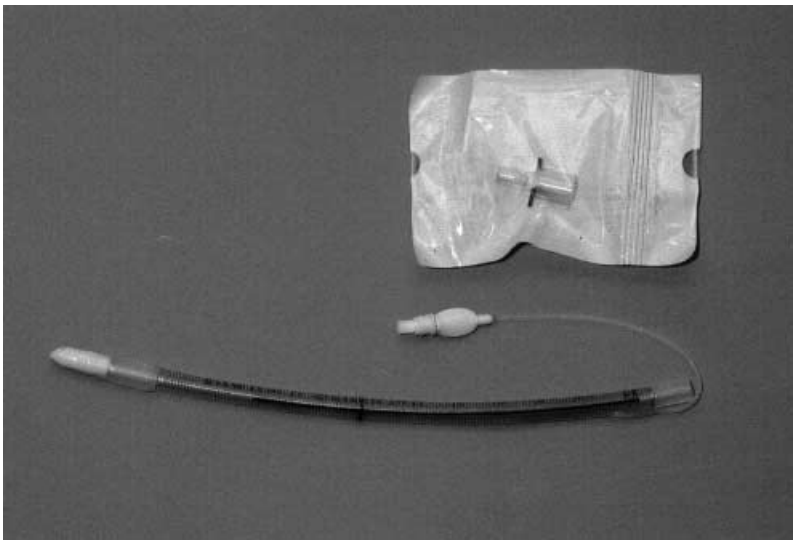

Figure 3 Photograph of armoured tracheal tube with removable connector (Euromedical ILM Endotracheal Tube – Introvent Orthofix).

of an associated head injury or facial swelling. In the series of 25 submental intubations reported by Caron, two patients had their submental tubes maintained postoperatively for approximately 30 h, because of facial swelling and fears of disrupting the facial reconstruction if the patient accidentally bit on the oral tube. No maxillomandibular fixation was used postoperatively in either patient to allow immediate access to the oral airway and when weaning and extubation were decided, the tracheal tube was removed by pulling it through the submental incision.

In summary, submental tracheal intubation is a useful alternative for airway management in selected patients with complex craniomaxillofacial injuries. It has a low morbidity and avoids some of the complications associated with nasal intubation and tracheostomy, whilst allowing unimpeded surgical access to the oral cavity and midface. It also avoids the need for a tube change half way through the operation if an oral tracheal tube was used initially. Good communication is essential, however, between the surgical and anaesthetic teams to minimise any potential complications.

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FORUM
Unwanted effects of morphine-6-glucuronide and morphine

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Summary
The active metabolite of morphine, morphine-6-glucuronide (M6G), may have fewer unwanted effects than morphine. We randomly allocated 144 women to receive either M6G or morphine as part of general anaesthesia for day case gynaecological laparoscopy. The incidence of nausea, vomiting, pain, sedation and skin rash, and severity of nausea, pain and sedation after surgery were recorded by direct observation in hospital, and by questionnaire until the next morning. Compared with the M6G group, patients who received morphine were more likely to report nausea in the first 2 h after surgery (odds ratio 2.9, CI 1.31–6.21) and to suffer it with greater severity. During the same time period, they were more likely to vomit and feel sleepy, but the intensity of pain and use of rescue analgesics were similar in both groups. The incidences of nausea, vomiting and the feeling of sleepiness continued to be greater in the morphine group during and after the journey home. The next morning, patients in the morphine group remained sleepier, but the incidence of nausea was similar for the two groups. M6G appears to have a better toxicity profile than morphine. More efficacy studies are needed to define accurately the analgesic potency of systemically administered M6G.

Keywords *Analgesics*: morphine morphine-6-glucuronide. *Vomiting*: incidence, nausea.

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Accepted: 30 June 2002

Morphine remains the standard analgesic for severe pain despite its emetogenic and sedative properties. After systemic administration, it is metabolised principally to morphine-3-glucuronide (M3G) which has no analgesic action [1] and to morphine-6-glucuronide (M6G), which has affinity for μ-receptors [2–5], and is more antinociceptive than morphine when administered intrathecally to humans [6, 7] or intracerebroventricularly to animals [5, 8, 9]. When administered systemically to animals, the relative potency of M6G to morphine is much closer [3, 5, 8], but in humans the evidence is conflicting, in part because of different methods of assessing analgesia [10–18]. M6G has a better toxicity profile for respiratory depression, nausea, sedation, and itching, in humans [11–13, 15, 18–20] if not for animals [9, 21, 22].

Postoperative nausea and vomiting (PONV) is commoner for women, for those prone to motion sickness and when opiates are administered [23, 24]. Using our model, described elsewhere [25, 26], to study PONV following day case laparoscopy, we compared PONV and other unwanted effects of M6G and morphine.

Methods

With Ethics Committee approval and written informed consent, we enrolled 144 healthy women, aged

18–65 years and scheduled for outpatient diagnostic pelvic laparoscopy. Patients were not studied if they were taking anti-emetic drugs, antidepressants or benzodiazepines started less than 3 weeks before surgery, were intolerant of non-steroidal anti-inflammatory drugs (NSAIDs), possibly were pregnant (checked on the day of surgery by a β HCG blood test), breast-feeding or had a body mass index greater than 31 $kg.m^{-2}$. Patients were asked to stop taking NSAIDs 24 h, and all analgesics 12 h before surgery.

Patients were randomly allocated in blocks of eight, to receive 120 $\mu g.kg^{-1}$ of either morphine sulphate or M6G at induction of a standardised general anaesthetic. The study drugs were blinded to patients, anaesthetists, recovery room staff and observers. Anaesthesia was induced with propofol 2–3 $mg.kg^{-1}$. Glycopyrronium 200 μg was given to prevent bradycardia, and vecuronium 70 $\mu g.kg^{-1}$ for muscle relaxation. A laryngeal mask airway was inserted, and the lungs ventilated with nitrous oxide 67% and enflurane in oxygen, to an end-tidal carbon dioxide of 4.5–5.0 kPa. At the end of surgery, muscle paralysis was reversed with neostigmine 2.5 mg, with glycopyrronium 500 μg. Rescue prescriptions were ketorolac 10–30 mg intravenously for pain, and prochlorperazine 12.5 mg i.m. for PONV.

Ten minutes after surgery ended, a 2-h period of immediate postoperative observation started. The incidences of nausea (the primary outcome measure), and of retching or vomiting, need for rescue anti-emetic or analgesia, and itching were recorded by one of three observers – the research nurse (CC) or research fellows (TM and BH). Patients were asked to assess the severity of nausea, intensity of pain and sedation using standard four-point ordinal scales. Observations were made at 10, 30, 60, 90, and 120 min into the study period. Patients were allowed home when able to walk unaided. Diclofenac (modified release) 75 mg twice daily and paracetamol 1 g as required, were given to be taken at home.

Immediately before discharge, patients were given a questionnaire, covering two time periods – from discharge until after the journey home, and from then until the next morning – to record nausea, vomiting or retching, 'sleepiness', itching and rash. Patients were telephoned to ensure completeness of data collection.

The sample size of 144, to allow for exclusion by protocol violations, was 115% of the number calculated to achieve a power of 80%, to detect a reduction of 50% at alpha = 0.05, with an expected incidence of the primary outcome measure of incidence of nausea taken as 40% [27]. Overall comparisons were performed using Fisher's exact or Chi-squared tests for categorical data, Student's unpaired *t*-test for normally distributed numerical data and Wilcoxon's rank sum test for non-parametric numerical data. The four-point ordinal scales for degrees of nausea, sedation, and intensity of pain in the first 2 h after surgery were compared using time-weighted areas under the curve. Confidence intervals were calculated for data for which a normal distribution was assumed. Tests were two-sided with a significance level of 5%. For patients receiving rescue analgesics or anti-emetics, and for missing observations, substitution was by last observation carried forward (LOCF).

Results

Of the 144 patients, six did not receive the study medication: five did not proceed to surgery, and one ampoule of medication was empty. The protocol was violated for three patients, all from the morphine group: one required additional opiate 60 min after surgery but was included in analysis by LOCF. Two were excluded from analysis: one had received additional peri-operative opiate and one underwent laparotomy. Of the remaining 136 patients, 66 received morphine and 70 received M6G. Demographic data were comparable for the groups (Table 1). All other results are shown in Table 2.

The first 2 h after surgery

Those who received morphine were 2.9 times more likely than the M6G group to report nausea, the primary outcome measure ($p < 0.01$, CI 1.31–6.21). They also reported it with greater severity, and for secondary outcome measures, those receiving morphine were 6.07 times more likely to vomit, 9.5 times more likely to receive escape anti-emetics, and by the end of this period, 2.4 times more likely to 'feel sleepy'. A trend for pain scores to be greater in the morphine group was not significant ($p = 0.21$), and the numbers receiving ketorolac in the 2 h after surgery were similar in the two groups.

During and after the journey home

The incidences of nausea, vomiting and feeling of sleepiness continued to be greater in the morphine group ($p < 0.001$, $p = 0.012$, $p < 0.001$, respectively). The morphine group was 18.19 times more likely to vomit during or after the journey home.

Table 1 Demographic data of patients included in final analysis. Values are mean (SD).

	Morphine	M6G
Age; years	31.1 (6.6)	30.5 (6.9)
Body Mass Index; $kg.m^{-2}$	23.10 (2.1)	23.0 (2.4)

Table 2 Outcome measures. All values of p are using Chi-square or *t*-tests, except ⋆Wilcoxon or ⋆⋆Fisher exact tests.

	Morphine			M6G					
	n	Yes (%)	No (%)	*n*	Yes (%)	No (%)	*p*	Odds ratio	95% C.I.
Nausea									
In first 2 h after surgery	66	26 (39.4)	40 (60.6)	70	13 (18.6)	57 (81.4)	< 0.01	2.85	1.31–6.21
Degree in first 2 h as median (range)	66	0.38 (0.13–1.83)		70	0.21 (0.04–0.88)		0.04*		
During/after journey home	66	37 (56.1)	29 (43.9)	70	9 (12.9)	61 (87.1)	< 0.001	8.65	3.69–20.28
Next morning	66	8 (12.1)	58 (87.9)	70	2 (2.9)	68 (97.1)	0.5**	4.69	0.96–22.97
Vomiting/retching									
In first 2 h after surgery	66	10 (15.2)	56 (84.8)	70	2 (2.9)	68 (97.1)	0.0120	6.07	3.77–10.31
Antiemetics given in first 2 h	66	8 (12.1)	58 (87.9)	70	1 (1.4)	69 (98.6)	0.015**	9.52	1.16–78.34
During/after journey home	66	23 (34.8)	43 (65.2)	70	2 (2.9)	68 (97.1)	< 0.001	18.19	4.08–81.06
Sedation									
Reported at end first of 2 h	66	19 (28.8)	47 (71.2)	70	10 (14.3)	60 (85.7)	0.039	2.43	1.03–5.71
Degree in first 2 h as mean (SD)	66	1.19 (0.60)		66	0.70 (0.42)		< 0.01		
During/after journey home	64	60 (93.7)	4 (6.3)	70	34 (49.1)	36 (50.9)	< 0.001	15.96	8.57–26.46
Next morning	65	35 (53.0)	30 (47.0)	70	16 (22.9)	54 (77.1)	< 0.001	3.93	1.88–8.26
Itching									
By end of day of surgery	66	14 (21.2)	52 (78.8)	70	6 (8.6)	64 (91.4)	0.038	2.87	1.03–8.00
Pain									
Intensity in first 2 h as mean (SD)	66	1.59 (0.80)		70	1.43 (0.78)		0.21		
Ketorolac administered	66	44 (66.7)	22 (33.3)	70	44 (62.9)	26 (37.1)	0.64	1.18	0.58–2.39

The morning after surgery

Patients in the morphine group remained sleepier than in the M6G group, but the difference in report of nausea was not significant. No patient vomited.

Discussion

We have demonstrated that when used as part of general anaesthesia for day case gynaecological laparoscopy, M6G causes significantly less nausea and other unwanted effects than does morphine. PONV, the incidence of which can reach 50% [27], is often the most distressing experience after day care surgery, causing unplanned admission to hospital. Ours is the largest scale study to show a favourable toxicity profile for humans for M6G as compared with morphine. It can be criticised because we used long-acting opiates for day case laparoscopy, and because of our assumptions about relative potency of morphine and M6G. At the time of our study, morphine was used routinely in our day case unit and elsewhere [28], although more recent practice is to use NSAIDs or shorter acting opiates [28] to avoid the side-effects of morphine. We chose the same dose for M6G as for morphine, on mass per body weight basis, using limited evidence available to us at the time [3, 5, 12, 28]. Recent estimates of relative potencies based on studies of animals [4, 10–12] and humans [14, 18] leave the matter unresolved, including to what extent the analgesic activity of systemically administered M6G is attributable to its permeation of the blood–brain barrier [14, 22, 29].

We examine our findings of fewer side-effects for M6G in the light of three possible scenarios. First, that morphine when administered intravenously is more potent than M6G; second, that they are equipotent; and third, that morphine is less potent than M6G. The first might explain the greater incidence of side-effects with morphine, but would not be supported by our findings of a trend for the intensity of pain to be greater in the morphine group, nor by the similar requirements in the two groups for ketorolac (escape analgesia) after surgery. Turning to the second and third scenarios, if morphine is of equal or lesser potency than M6G, it follows that M6G has an excellent profile with regard to the common unwanted side-effects that follow the use of morphine. This conclusion needs to be tested in other situations, including surgery where the requirement for drugs such as morphine remains clearly established, and ideally where analgesia is required for a longer period of time than in the present study.

Acknowledgements

This study was funded by Nycomed Imaging AS. We also thank Cenes-UK, our day case theatre staff and anaesthetists, Professor Alan Aitkenhead and Dr Ravi Mahajan.

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FORUM

Tracheal intubating conditions using propofol and remifentanil target-controlled infusions

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Summary

Using target-controlled infusions (TCI) we aimed to determine the most appropriate dose of remifentanil required for intubation, using a steady effect-site concentration of propofol and without the use of neuromuscular blocking drugs. Sixty ASA I–II patients presenting for elective surgery were randomly allocated to one of three groups. Anaesthesia was induced in all patients using a target-controlled infusion of propofol 6.5 $\mu g.ml^{-1}$. This was reduced to 3 $\mu g.ml^{-1}$ after 1 min. Each group received a different TCI of remifentanil, 19, 15 or 11 $ng.ml^{-1}$, which was reduced to 10, 8 or 6 $ng.ml^{-1}$, respectively, after 1 min. Laryngoscopy and intubation were attempted at 4 min. Laryngoscopy and ease of intubation were assessed using a standard scoring system. Intubation was considered satisfactory in 75% of patients in groups 1 and 2 and 35% of patients in group 3. Intubation was successful in 20/20, 19/20 and 15/20 patients in groups 1, 2 and 3, respectively. Pulse oximetry, heart rate and noninvasive arterial pressure were measured pre-induction, and at intervals until after laryngoscopy and intubation. Mean arterial pressure (MAP) and heart rate decreased following induction of anaesthesia in all groups, which was statistically significant. Following laryngoscopy, MAP and heart rate increased, but were significantly less than the corresponding baseline values.

Keywords *Anaesthetic techniques*: intravenous. *Anaesthetics, intravenous*: propofol. *Analgesics*: remifentanil.

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Accepted: 16 July 2002

Remifentanil is a powerful opioid, with a rapid onset of action. It is hydrolysed by nonspecific blood and tissue esterases and has a context-sensitive half-time of ≈ 3 min [1]. It is well suited to target-controlled infusion (TCI), as it does not accumulate following prolonged infusions. Propofol and remifentanil have been shown to provide good intubating conditions without the use of neuromuscular blocking drugs [2–4]. Laryngoscopy and intubation are associated with haemodynamic pressor responses, which can have adverse effects [5, 6]. Remifentanil can attenuate this response when combined with propofol or sodium thiopental [7, 8]. We aimed to determine the most appropriate dose of remifentanil required for intubation using a steady effect-site concentration of propofol, and whether this would avoid the pressor response associated with laryngoscopy.

Patients and methods

Following local ethics committee approval and written informed consent, 60 ASA I–II patients were enrolled into the study. All patients were scheduled for elective surgery, which required tracheal intubation. They were aged between 18 and 67 years and with a body mass index of $< 30\ kg.m^{-2}$. Exclusion criteria included Mallampati grade 3–4, previously documented difficult intubation,

gastro-oesophageal reflux, reactive airways disease and substance abuse.

The patients received 20 mg of oral temazepam 1 h pre-operatively, and were randomly allocated into one of three groups. In the anaesthetic room, routine monitoring was established. Pulse oximetry, heart rate and noninvasive arterial pressure was measured prior to induction of anaesthesia and at intervals of 1 min throughout the study period.

All patients were pre-oxygenated prior to induction of anaesthesia. Anaesthesia was induced in all groups using a TCI of propofol (Graseby 3500 pump) of 6.5 $\mu g.ml^{-1}$. At the same time, a TCI of remifentanil (IVAC pump from Alaris Medical Systems programmed with pharmacokinetic data for remifentanil) was started [9]. Groups 1, 2 and 3 had a target blood concentration of 19, 15 and 11 $ng.ml^{-1}$, respectively. After 1 min, the target concentration of propofol was reduced to 3 $\mu g.ml^{-1}$ in the three groups, and the target concentration of remifentanil was reduced to 10, 8 and 6 $ng.ml^{-1}$, in groups 1, 2 and 3, respectively. After 3 min, the target and effect-site concentrations had equilibrated.

The patients' lungs were inflated manually with an air/oxygen mixture using a Bain circuit. A consultant anaesthetist then attempted laryngoscopy and intubation 4 min following induction of anaesthesia. Intubating conditions were scored using a system devised by Helbo-Hansen *et al.* [10], and which has been used in similar studies [3, 11]. Ease of ventilation, jaw relaxation, ease of laryngoscopy, degree of coughing and patient movement were all assessed (Table 1).

A score of 1–2 in all intubating conditions was considered acceptable, whereas a score of 3–4 in any of the intubating conditions was deemed unacceptable. If intubation was considered impossible then 0.6 $mg.kg^{-1}$, rocuronium was administered. Once the trachea was intubated the cuff was inflated. Ephedrine was administered if the mean arterial pressure decreased below 50 mmHg, and atropine if the heart rate decreased below 45 $beat.min^{-1}$ for longer than 60 s.

Parametric data from each group were analysed as a random effects linear model. Nonparametric data were analysed using chi-squared analysis. A p-value of < 0.05 was considered to be significant. Data were analysed using DATA DESK RELEASE 6.1.1 and STATA/SE RELEASE 7 software.

Results

Sixty patients were successfully enrolled into the study, their mean ages were 39 [range 18–56], 41[19–67] and 42[20–63] years in groups 1, 2 and 3, respectively. Mean (SD) weights were 71 (13.6), 65 (8.9) and 65 (10.6) kg in groups 1, 2 and 3, respectively. Six of the 60 patients were male. The fact that the majority of operating sessions were gynaecological accounts for the prevalence of female patients.

All patients' lungs were easily ventilated prior to intubation except for one patient, in group 3, who required a Guedel airway to assist ventilation.

Group 1: intubation was successful in all patients, while conditions were deemed satisfactory in 15/20 (75%) patients. Of the five patients in whom conditions were considered unacceptable, two had moving vocal cords and three coughed following inflation of the tracheal tube cuff.

Group 2: intubation was successful in 19/20 patients, with satisfactory conditions achieved in 15/20 (75%) patients. Two patients had closing vocal cords, two had jaw stiffness and one required the administration of a neuromuscular blocking drug, due to closed vocal cords.

Group 3: intubation was successful in 16/20 patients, while only 7/20 (35%) patients were deemed to have satisfactory conditions. Five patients had closing vocal cords, four coughed on inflation of the tracheal tube cuff, and four others required a neuromuscular blocking drug for closed vocal cords. There was a significant difference between the intubation conditions achieved in groups 1 and 2 and those achieved in group 3 ($p = 0.024$).

There were no significant differences in haemodynamic variables among the groups prior to induction. Mean arterial pressure (MAP) decreased in all groups following induction of anaesthesia (Table 2).

Following laryngoscopy and intubation, MAP and heart rate increased to values that remained significantly lower than the corresponding baseline values (Table 3).

Two patients, in group 2, required ephedrine 6 mg to treat a MAP of 48 and 44 mmHg, respectively, before

Table 1 Intubation scoring system.

Jaw relaxation	Complete	Tone	Stiff	Rigid
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Movement	None	Slight	Moderate	Severe

Table 2 Mean arterial pressure (SD) at pre-induction (baseline), 1 and 3 min after induction and post laryngoscopy/intubation.

	Baseline	1 min	3 min	Post laryngoscopy
Group 1	97 (14)	85 (16)	65 (12)	69 (13)
Group 2	93 (10)	84 (15)	60 (9)	72 (11)
Group 3	100 (11)	87 (14)	68 (12)	75 (13)

Table 3 Mean heart rate (SD) at pre-induction (baseline), 1 and 3 min after induction and post laryngoscopy/intubation.

	Baseline	1 min	3 min	Post laryngoscopy
Group 1	82 (16)	72 (11)	63 (8)	67 (10)
Group 2	73 (10)	71 (8)	62 (7)	67 (11)
Group 3	83 (14)	75 (11)	64 (7)	64 (7)

intubation. In group 1, two patients required atropine 300 μg when the heart rate decreased below 45 beat.min^{-1}. Patients in group 3 did not require any intervention. There was a highly significant difference in the haemodynamic variables between time periods ($p < 0.0001$), but overall there was no significant difference among treatment groups ($p = 0.156$).

Discussion

Continuous infusions can provide stable concentrations of drug administration compared with intermittent doses that may be associated with greater haemodynamic instability. TCI allows a calculated amount of drug to be delivered smoothly and that concentration can be adjusted rapidly and easily in a controlled manner. Effect-site concentrations represent the estimated amount of drug at the site of action in the brain [12]. There is a delay between the equilibration of the blood and the effect-site as the drug undergoes redistribution. In this study, intubation was attempted at 4 min following induction to allow equilibration to take place between the blood and the effect site. Selecting a high target concentration initially increases the concentration in the central compartment and speeds up the movement of drug into the effect site. The concentrations selected produce equilibration within 4 min from the start of the infusions.

Many studies have looked at the most appropriate dose of opioid along with propofol for use in induction and intubation without the use of neuromuscular blocking drugs [2–4]. Avoiding neuromuscular blocking drugs may be beneficial, or necessary, in some patients, especially if surgery does not require muscle relaxation to facilitate surgery. Alfentanil 30–60 μg.kg^{-1} has been shown to provide good conditions for tracheal intubation along with propofol 2 mg.kg^{-1} [13]. Comparable results have been obtained using remifentanil or alfentanil. However, remifentanil is more suited to infusions as it has a higher clearance and a smaller steady-state distribution volume, leading to a rapid recovery after prolonged infusion [1].

In our study, seven patients coughed after introduction of the tracheal tube, usually during inflation of the cuff. In other studies, the cuff was inflated slowly which may reduce the incidence of coughing [2, 4, 13]. The addition of intravenous lidocaine can reduce the incidence of coughing, as well as attenuate the haemodynamic response to laryngoscopy and intubation as shown by Davidson *et al.* [14].

The beneficial effect of remifentanil in attenuating the pressor response to intubation has been studied. McAtamney *et al.* [15] studied the effect of single doses of remifentanil with thiopental and concluded that 1 μg.kg^{-1} attenuated the response. Woods *et al.* [3] and colleagues studied propofol 2 mg.kg^{-1} with remifentanil for intubation without neuromuscular blocking drugs. They demonstrated a decrease in arterial pressure and heart rate with remifentanil 1 μg.kg^{-1} and lidocaine, and with remifentanil 2 μg.kg^{-1}. As in our study, patients required ephedrine for decreases in MAP. However, after one dose of ephedrine and laryngoscopy, the arterial pressure returned to within normal limits. They concluded that a 30 s infusion of 2 μg.kg^{-1} of remifentanil would achieve a peak blood concentration in 90–120 s. In our study, the lowest concentration of remifentanil 6 ng.ml^{-1} did not achieve satisfactory conditions for intubation but did attenuate the pressor response to intubation to the same extent as group 1 and 2. All patients in our study were ASA I–II and undergoing elective procedures. However, caution should be used in the elderly or compromised patient as the combination of remifentanil and propofol may produce bradycardia and hypotension. The TCI were commenced and adjusted at the same time in our study. The timing of induction agent and opioid administration is important as it can lead to different results.

In conclusion, TCI of propofol and remifentanil can provide satisfactory conditions for intubation, without the use of muscle relaxants. TCI allow for easy adjustment of anaesthetic depth, and can attenuate the haemodynamic response to laryngoscopy. We consider that an effect-site concentration of remifentanil 8 ng.ml^{-1} along with an effect-site concentration of propofol 3 μg.ml^{-1} may provide satisfactory conditions for intubation, while avoiding major adverse haemodynamic effects.

Acknowledgements

We would like to thank the medical and nursing staff at the Vale of Leven Hospital for their assistance during this study. The results were presented in part at the Glasgow Anaesthetic Research Meeting, May 2000 and at the SIVA UK meeting in Belfast, November 2000.

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FORUM

Combined use of esmolol and nicardipine to blunt the haemodynamic changes following laryngoscopy and tracheal intubation*

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Summary

We examined the effect of different combinations of esmolol and nicardipine upon the circulatory response to tracheal intubation. One hundred patients were randomly allocated into five groups of twenty to receive pretreatments of saline or different combinations of esmolol (0.5 or 1.0 $mg.kg^{-1}$) and nicardipine (15 or 30 $\mu g.kg^{-1}$). Significant tachycardia persisted over a 5-min period after

intubation in all five groups compared with baseline levels ($p < 0.05$). Patients receiving esmolol 1.0 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} showed no significant change in systolic blood pressure after tracheal intubation compared with baseline and significant lower peak systolic blood pressure than those receiving saline ($p = 0.023$).

Keywords *Intubation*: tracheal. *Sympathetic nervous system*: α adrenergic antagonists, esmolol. *Calcium-channel blockers*: nicardipine.

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**Presented in part at the 10th European Society of Anaesthesiologists' Anniversary Meeting/24th European Academy of Anaesthesiologists' Annual Meeting, Nice, April 2002.*
Accepted: 2 September 2002

Instrumentation of the pharynx and tracheal intubation may result in tachycardia, hypertension and elevated plasma catecholamine concentrations that may evoke life-threatening conditions among susceptible individuals, especially those with cardiovascular or cerebrovascular disease [1, 2]. Various pharmacological attempts have been made to blunt such responses, including local anaesthetics [3], α- and β-blocking agents [4], vasodilators [5] and opioids [6]. Esmolol is a water-soluble, cardioselective, ultrashort-acting β-adrenergic antagonist [7–10]. Its pharmacological properties of rapid onset and offset of action are particularly advantageous in obtunding the haemodynamic response to laryngoscopy and tracheal intubation [7–10].

Nicardipine is a dihydropyridine derivative which acts as a calcium-channel blocker. The onset of action of nicardipine is rapid and its duration is fairly short; nicardipine protects against the effects of cardiac ischaemia by increasing coronary perfusion, oxygen delivery and overall aerobic metabolism [11]. Previously, nicardipine has been administered intravenously during anaesthesia with isoflurane, fentanyl and halothane, with no untoward effects [12–14]. Thus nicardipine appears to be an appropriate agent for attenuating the circulatory responses to laryngoscopy and tracheal intubation.

Combined use of a half dose of esmolol and of nicardipine has previously been shown to be more effective in blunting the haemodynamic response to laryngoscopy and intubation than the use of either drug alone [15]. Atlee *et al.* [15] reported in 2000 that the combination of esmolol 0.5 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} blunted the peak increase in blood pressure but did not prevent an increase in heart rate following laryngoscopy and intubation, whereas esmolol 1 mg.kg^{-1} with nicardipine 30 μg.kg^{-1} was suggested as being sufficient to blunt both blood pressure and heart rate changes [15]. However, this study was limited by the absence of dose ranging for combinations of esmolol and nicardipine. Therefore, we evaluated the effect of four combinations of different doses of esmolol and nicardipine in attenuating the cardiovascular responses to laryngoscopy and intubation.

Methods

Following institutional ethical review and written informed consent, 100 normotensive patients of ASA status I–II scheduled for elective non-cardiac surgery were entered into a double-blind, randomised, placebo-controlled study. None of the subjects demonstrated any history or signs of cardiopulmonary disease or any contraindication for the use of β-blockers or calcium-channel blockers, and no patient was taking any cardiac or respiratory medication. The patients were randomly allocated (using computer-generated random numbers) into 5 groups of 20, to receive saline, esmolol 0.5 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E0.5–N15 group), esmolol 1.0 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E1–N15 group), esmolol 0.5 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} (E0.5–N30 group) or esmolol 1.0 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} (E1–N30 group). A nurse-anaesthetist, otherwise not participating in the investigation (blindly) prepared the study drugs in ready-to-use syringes so as to ensure that the study was double-blinded.

None of the patients received any premedication. On arrival in the operating theatre, three-lead ECG monitoring, pulse oximetry and non-invasive blood pressure monitoring were established and baseline values obtained. Following this, the study drug was administered i.v., followed 2 min later by thiopental 5 mg.kg^{-1}, fentanyl 1.5 μg.kg^{-1} and succinylcholine 1.5 mg.kg^{-1}. Direct laryngoscopy was performed 1 min after administration of succinylcholine. Haemodynamic data were recorded again immediately before and at 1, 2, 3 and 5 min after

tracheal intubation. Each intubation was performed by an experienced anaesthetist and accomplished within 20 s. Following intubation, ventilation was controlled with 50% nitrous oxide in oxygen for 5 min, following which sevoflurane was added.

Prior power analysis, based on a ratio of the difference between the means and standard deviation of 0.8, $\alpha = 0.05$ and $\beta = 0.2$ for peak systolic blood pressure and heart rate, suggested that a sample size of 20 would be adequate. Data were analysed using one-way ANOVA for comparison among and within groups. Tukey's pairwise comparison and Bonferroni's correction were performed when significant differences were found after ANOVA. Results were considered significant when $p < 0.05$.

Results

One hundred and five patients were included in the study. Five patients were not studied further because intubation took more than 20 s. The five groups were similar with regard to age, sex, height and weight (Table 1).

Statistically significant tachycardia persisted for 5 min after laryngoscopy and intubation in all groups compared with baseline levels except for the saline group (Fig. 1). Heart rate was higher in the E0.5–N30 group than in the other groups at 1–3 min (Fig. 1). No significant differences in heart rate were noted at any time between the saline group and the E0.5–N15, E1–N15 and E1–N30 groups (Fig. 1).

Systolic blood pressure decreased in all groups after induction of anaesthesia and administration of the study drug, with a smaller reduction in the saline group than in the other groups (Fig. 2). Systolic pressure increased at 1–3 min after laryngoscopy and intubation in all groups except E1–N30 (Fig. 2). Peak systolic pressure was higher in the saline group [164 (25) mmHg] than in the E1–N30 group [135 (18) mmHg; $p = 0.023$]. No episodes of bradycardia (heart rate < 50 beat.min^{-1}) or hypotension (systolic pressure < 90 mmHg) were observed during the study in any group.

Table 1 Characteristics of patients receiving saline, esmolol 0.5 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E0.5–N15), esmolol 1.0 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E1–N15), esmolol 0.5 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} (E0.5–N30) or esmolol 1.0 mg.kg^{-1} and nicardipine 30 μgkg^{-1} (E1–N30) before laryngoscopy and tracheal intubation.

	Saline (*n* = 20)	**E0.5**–N15 (*n* = 20)	**E1**–N15 (*n* = 20)	**E0.5**–N30 (*n* = 20)	**E1**–N30 (*n* = 20)
Sex; M/F	12/8	11/9	11/9	10/10	9/11
Age; years	37.7 (11)	41.5 (13.4)	42.5 (15.5)	38.7 (15.4)	39.5 (13.5)
Height; cm	164.7 (7.1)	163.9 (6.9)	161.5 (6.4)	164.3 (9.7)	167.2 (9.3)
Weight; kg	67.3 (9.3)	65 (12.5)	62.8 (9)	65.5 (8.5)	66.5 (11.3)

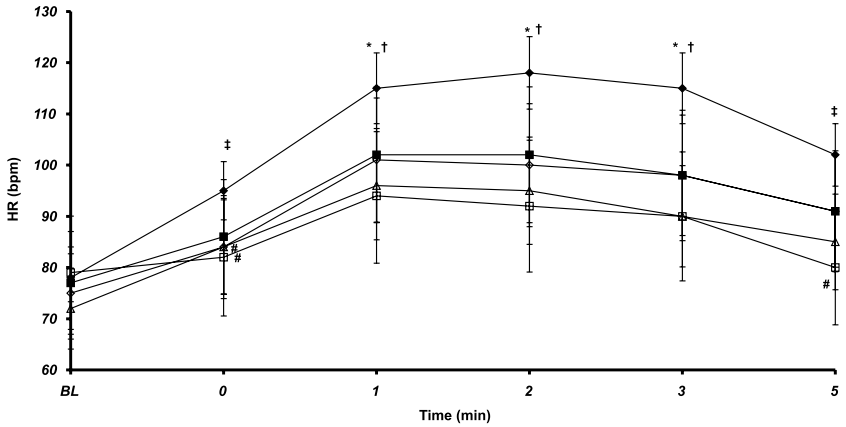

Figure 1 Heart rate (HR) in patients receiving saline (□), esmolol 0.5 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E0.5–N15; ■), esmolol 1.0 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E1–N15; ◇), esmolol 0.5 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} (E0.5–N30; ◆) or esmolol 1.0 mgkg^{-1} and nicardipine 30 μgkg^{-1} (E1–N30; △) before and after laryngoscopy and tracheal intubation (at time 0). Values are mean (SD). ⋆$p < 0.05$ compared with baseline (BL) values in all groups; †$p < 0.05$ E0.5–N30 vs. the other groups; ‡$p < 0.05$ compared with baseline values in all groups except the saline group; #$p < 0.05$ vs. E0.5–N30.

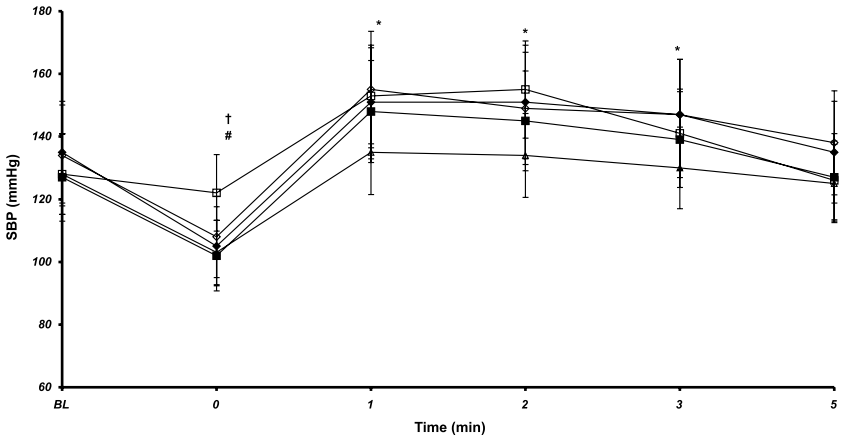

Figure 2 Systolic blood pressure (SBP) in patients receiving saline (□), esmolol 0.5 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E0.5–N15; ■), esmolol 1.0 mg.kg^{-1} and nicardipine 15 μg.kg^{-1} (E1–N15; ◇), esmolol 0.5 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} (E0.5–N30; ◆) or esmolol 1.0 mg.kg^{-1} and nicardipine 30 μg.kg^{-1} (E1–N30; △) before and after laryngoscopy and tracheal intubation (at time 0). Values are mean (SD). ⋆$p < 0.05$ compared with baseline (BL) values in all groups except E1–N30; †$p < 0.05$ compared with baseline values in all groups; #$p < 0.05$ saline vs. the other groups.

Discussion

We found that none of the tested combinations of esmolol and nicardipine were effective at blunting the haemodynamic response to laryngoscopy and intubation, apart from one specific combination (esmolol 1.0 mg.kg^{-1} and nicardipine 30 μg.kg^{-1}) which was able to blunt the increase in systolic blood pressure but not heart rate. Compared with saline, this combination of esmolol and nicardipine also resulted in a lower peak systolic pressure. These doses of esmolol and nicardipine are somewhat higher than the 'effective' doses of the two agents specified in a previous study: 0.5 mg.kg^{-1} and 15 μg.kg^{-1}, respectively [15]. This observation may be associated with a variety of factors, including the time between administration of the study drug and laryngoscopy, the presence/absence of any premedication, and our inclusion of generally healthier patients.

Cardiovascular stimulation from laryngoscopy and intubation is short-lived, as are the haemodynamic effects of esmolol and nicardipine. The distribution time for these drugs is ≈1–3 min following intravenous administration, with an elimination half-life of around 10 min [16–18]. We chose our time interval between administration of the study drugs and laryngoscopy based upon a previous study [15]. Ebert *et al.* [10] and Kindler *et al.* [19] have suggested that the increase in heart rate elicited by laryngoscopy and intubation could be prevented by esmolol 1–2 mg.kg^{-1} administered 90 s before laryngoscopy. Therefore, in our study, the delay between administration of esmolol and nicardipine and the time of intubation might have been too long, such that the peak effect of the drugs may have been missed.

The optimal dose of esmolol to obtund the haemodynamic responses to tracheal intubation has been a subject of discussion. Previously, some investigators have reported that a higher dose of esmolol than was used in our study was necessary [7, 8] although other workers have not concurred [9, 10]. Indeed, some authors have found 100 mg esmolol as effective as 200 mg [9, 10]. The dose of esmolol we elected to use was similar to that studied by Kindler *et al.* [19]. However, patients in that study also received premedication with 3 mg bromazepam orally, and maintenance of anaesthesia was using 70% nitrous oxide in oxygen for 5 min. Previous investigators have demonstrated that benzodiazepine premedication is effective in modifying cardiovascular responses intraoperatively [20]. The patients in our study received no premedication and maintenance of anaesthesia incorporated 50% nitrous oxide in oxygen for the first 5 min of anaesthesia. In addition to premedication, the patients' baseline haemodynamic status was another factor which could have influenced the cardiovascular response to tracheal intubation. In a 1991 Canadian multicentre trial involving 548 patients, Miller *et al.* [21] reported that the maximal changes in heart rate and systolic blood pressure were inversely related to their baseline values, such that patients whose heart rate and blood pressure were low before induction of anaesthesia experienced the largest increase for either variable in response to instrumentation of the airway. Conversely, patients whose heart rate and blood pressure were elevated before induction of anaes-

thesia, perhaps arising as a result of greater sympathetic tone and increased anxiety, tended to develop smaller absolute increases in both these variables. Thus, because our patients' heart rates and blood pressures were not elevated before anaesthesia, they may have experienced a larger haemodynamic response.

Our study has demonstrated that the increase in heart rate associated with laryngoscopy and tracheal intubation cannot be blunted effectively by any of the combinations of esmolol and nicardipine we used. Further, we found a significant increase in heart rate for the E0.5–N30 group compared with the other four groups. Previously, nicardipine has been shown to elicit a dose-dependent, reflex tachycardia [22], and the tachycardia we observed may be related to the more substantial dose of nicardipine in this group. The increase in heart rate following administration of nicardipine has been shown to be greater in normotensive patients than in hypertensive patients, possibly due to nicardipine-induced sensitivity of the baroreflex-mediated response among normotensive patients [23], and this may also have been important in our patients.

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