Low-dose ketamine with clonidine and midazolam for adult day care surgery

EDITOR:
The ideal anaesthetic for day-surgery procedures should give quick recovery without pain, nausea or vomiting and ensure a rapid return to preoperative mental state with rapid discharge and patient satisfaction.

Ketamine was introduced into clinical practice nearly 40 yr ago but its use has declined. It nevertheless remains in regular use in certain surgical disciplines, e.g. paediatrics, plastic and burn surgery, during emergencies or during short diagnostic procedures. However, when administered to adult patients as the sole anaesthetic it frequently causes emergence reactions characterized by anxiety and hallucinations. A number of agents, including midazolam and clonidine, have been used to reduce or prevent these reactions.

The aim of the present study was to test whether the combination of low-dose ketamine with midazolam, clonidine and ketorolac but without opioid administration, could provide adequate anaesthesia for interventions with low-to-medium pain potential performed on a day-surgery basis. This included breast surgery, laparoscopy, superficial excision of minor lesions, thoracoscopy, appendicectomy and proctological surgery.

Five hundred patients, (172 males and 328 females) ASA Grade I–II, were enrolled in the study. All gave written, informed consent and were instructed in the use of the visual analogue scale (VAS). Overall mean age was 53.9 (SD 12.2) yr and mean weight 76.1 (SD 22.5) kg. Sedation was assessed using the Observer’s Assessment of Alertness/Sedation Scale (OAA/S) [1] and cognitive function was assessed with the Mini Mental State Examination [2]. The Profile of Mood State was used to assess mood [3].

Heart rate (HR), respiratory rate, oxygen saturation and arterial pressure were measured before and during surgery and for 1 h afterwards. Before induction of anaesthesia with propofol 2 mg kg⁻¹, patients were given atropine 0.01 mg kg⁻¹, midazolam 0.03–0.05 mg kg⁻¹ and ketamine 0.4 mg kg⁻¹ all intravenously (i.v.). All patients received nitrous oxide 65% in oxygen. Muscle relaxation was obtained with suxamethonium (1.0–1.5 mg kg⁻¹) or vecuronium (0.1 mg kg⁻¹) for tracheal intubation and maintained with vecuronium. After tracheal intubation patients were given clonidine 150 µg i.v. If depth of anaesthesia was not adequate (blood pressure, BP or HR >20% of the preinduction values, lacrimation and sweating) patients were given ketamine 0.4–0.6 mg kg⁻¹ (maximum total dose 1 mg kg⁻¹) or bolus injections of propofol 0.5 mg kg⁻¹. The last ketamine administration was at least 1 h before the end of surgery. Ketorolac 30 mg and dexamethasone 8 mg were administered i.v. 30 min before wound closure. Total dose of ketamine used was 0.6 (SD 0.2) mg kg⁻¹. At the end of the procedure, neuromuscular block was reversed using neostigmine, nitrous oxide was discontinued and the interval from this time to eye opening was recorded. Overall mean duration of surgery and anaesthesia were 121.4 (SD 60.1) min and 146.4 (SD 63.5) min, respectively.

Time from discontinuation of nitrous oxide to eye opening was 176.9 (SD 106.1) s. Immediately after extubation and every 10 min thereafter, VAS scores for pain, sleepiness and nausea, OAA/S, and Aldrete score [4] were measured. In the first postoperative hour, ketorolac 0.3–0.6 mg kg⁻¹ was administered if VAS for pain was >30. Patients were discharged from the recovery room when two consecutive Aldrete scores were ≥9 and all VAS scores were <30. At this time, the Profile of Mood State and Mini Mental State examination were repeated and patients were asked whether they felt strange or disoriented.

Vital signs, nausea, pain, sleepiness and readiness for discharge from the hospital were assessed at 2, 3 and 4 h from the end of surgery. Patients were judged ‘ready for discharge’ (even if not actually dismissed from the hospital) when they had stable vital signs: no nausea, were oriented, able to ambulate unassisted

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Values are expressed as mean ± SD.

Table 1. Physiological parameters and postoperative evaluation at different times from awakening.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Awakening</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>72.1 ± 9.2</td>
<td>77.3 ± 11.8</td>
<td>68.6 ± 9.2</td>
<td>65.9 ± 7.2</td>
<td>66.7 ± 8.1</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>97.4 ± 11.9</td>
<td>106.0 ± 14.3</td>
<td>97.9 ± 13.1</td>
<td>95.0 ± 14.4</td>
<td>93.1 ± 13.8</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>14.4 ± 3.0</td>
<td>16.6 ± 3.9</td>
<td>16.1 ± 3.9</td>
<td>16.1 ± 3.1</td>
<td>15.7 ± 3.1</td>
</tr>
<tr>
<td>OAA/S</td>
<td>5.0 ± 0.0</td>
<td>4.5 ± 0.8</td>
<td>4.9 ± 0.3</td>
<td>4.9 ± 0.2</td>
<td>5.0 ± 0.2</td>
</tr>
<tr>
<td>Aldrete score</td>
<td>3.8 ± 12.2</td>
<td>9.2 ± 1.0</td>
<td>9.4 ± 0.6</td>
<td>9.6 ± 0.5</td>
<td>9.7 ± 0.5</td>
</tr>
<tr>
<td>VAS pain</td>
<td>4.8 ± 9.3</td>
<td>37.7 ± 33.2</td>
<td>35.3 ± 29.3</td>
<td>28.5 ± 27.6</td>
<td>24.4 ± 25.7</td>
</tr>
<tr>
<td>VAS sedation</td>
<td>1.8 ± 7.1</td>
<td>6.5 ± 18.9</td>
<td>4.4 ± 12.2</td>
<td>3.5 ± 10.3</td>
<td>2.8 ± 7.5</td>
</tr>
<tr>
<td>VAS nausea</td>
<td>10.3 ± 2.8</td>
<td>7.5 ± 3.9</td>
<td>8.1 ± 3.1</td>
<td>8.1 ± 3.1</td>
<td>8.1 ± 3.1</td>
</tr>
<tr>
<td>VAS vomiting</td>
<td>12.2 ± 3.5</td>
<td>13.8 ± 3.5</td>
<td>10.3 ± 3.5</td>
<td>10.3 ± 3.5</td>
<td>10.3 ± 3.5</td>
</tr>
</tbody>
</table>

and to drink. Eighteen to 24 h after the end of surgery, the Iowa satisfaction scale questionnaire [5] was administered to investigate if undesired effects in the perioperative period could be attributed to anaesthesia or surgery. Shortly after awakening, physiological parameters returned to preoperative baseline values demonstrating rapid recovery from anaesthesia. In the first 30 min, the VAS for nausea and pain were low, while VAS for sleepiness was moderately high, albeit constantly decreasing (Table 1). Only 78 patients (16%) required additional ketorolac in the immediate postoperative period. The postoperative Mini Mental Status Examination showed a non-significant reduction (0.88 points). Mood decreased postoperatively (−1.04) with the patients complaining most frequently of tiredness. Finally, 50% reported feeling strange and 35% disoriented.

After 30 min, the defined minimum time of stay in the recovery room, 26% of the patients were not eligible for discharge, however, all the patients left the recovery room within 1 h. In all patients, the limiting parameter for discharge was the VAS score for sleepiness.

No patients suffered from hallucinations or emergence reactions, and only 26% attributed undesired effects to anaesthesia. Finally, postoperative evaluation showed that all patients would have been able to leave the hospital within 6 h after the end of surgery; 89% of them within 4 h.

It is our experience that the combination of low-dose ketamine, clonidine, midazolam and ketorolac provides adequate analgesia with cardiovascular stability during surgery. Further advantages of this combination are the absence of respiratory depression, rapid awakening, rapid return of HR and BP to preoperative values, a low incidence of nausea and vomiting, and an analgesic effect lasting into the immediate postoperative period. There was a high rate of patient satisfaction (Iowa Score 23.4 ± 5.9).

The results of our study demonstrate that good postoperative pain control can be achieved without opioids or postoperative nausea and vomiting. Clonidine and midazolam administered during anaesthesia appear to have minimized the cardiovascular and psychotomimetic effects of ketamine [6,7]. Our results suggest that low-dose ketamine when combined with other drugs might represent a suitable technique for day care surgery.

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References

Ketamine pretreatment with venous occlusion attenuates pain on injection with propofol

EDITOR:
Injection of propofol into a peripheral vein is associated with a high incidence of local pain and discomfort. Different manoeuvres have been tried to reduce this pain, but with varying success. The addition of a small dose of lidocaine to propofol is the most commonly used technique, but this does not eliminate the pain in all cases [1]. Lidocaine also has its maximum effect when given as a pretreatment with a venous tourniquet occluding the proximal part of the arm [1]. Recent work suggests that prior administration of ketamine 10 mg, 30 s before propofol (without temporary venous occlusion) reduces the propofol associated pain [2]. In this prospective, randomized, double blind, placebo-controlled study, we further investigated whether a small dose of ketamine reduces pain on injection with propofol in the same magnitude as does lidocaine with a tourniquet. After obtaining institutional Ethics Committee approval and informed written consent, we studied 150 adult ASA I or II patients aged 20–60 yr, who were scheduled for elective surgery. Patients taking regular analgesics or sedatives, suffering from acute or chronic pain syndromes, or any neurological diseases, thrombophlebitis, known allergy to local anaesthetics, propofol or ketamine, were excluded. All patients were premedicated with diazepam 10 mg orally 90–120 min before induction of anaesthesia. When the patient arrived in the operating room, routine monitoring was applied and, following baseline homodynamic values, a 20-G IV cannula was inserted on the dorsum of the non-dominant hand without the use of local anaesthetic. The cannula was flushed with normal saline. No other solution was injected before the induction of anaesthesia with propofol. Patients were randomly assigned using a sealed envelope technique to one of three groups: Group saline (n = 50) received physiological saline 2 mL with venous occlusion for 1 min; Group lidocaine (n = 50) received lidocaine 20 mg in 2 mL saline with venous occlusion for 1 min; Group ketamine (n = 50) received ketamine 10 mg in 2 mL saline with venous occlusion for 1 min. Venous occlusion was performed using a rubber tourniquet placed on the upper arm after elevating the arm for 30 s for gravity drainage of venous blood [3]. Before induction of anaesthesia, the patients were informed that they would be receiving an intravenous (i.v.) anaesthetic that may cause pain in the forearm. Thirty seconds after the pretreatment bolus, the occlusion was released and propofol 2.5 mg kg⁻¹ was administered through the same 20-G catheter at the rate of 1 mL s⁻¹. Fifteen seconds after injection of 25% of the dose of propofol, patients were asked by an independent, second anaesthesiologist to grade their pain in accordance with the criteria shown in Table 1. After assessment of the pain intensity, the rest of the dose of propofol was given and anaesthesia was continued as planned. Statistical comparisons were carried out using ANOVA and the Kruskal–Wallis test where appropriate; *P < 0.05 was considered significant. The distribution of pain scores in each group is shown in Table 2. With saline, 40 of 50 patients (80%) experienced pain on propofol injection, and in 14 of those, pain was graded as severe (28%). After lidocaine, five of 50 patients (10%) experienced pain; this was significantly less than with the control group (P < 0.0001). After ketamine, six of 50 patients (12%) experienced pain; this, again, was significantly less than with the control group (P < 0.0001). No statistically significant difference was noted between the ketamine and lidocaine groups (P > 0.05). Pain intensity was significantly less in patients who received ketamine and lidocaine as compared to saline (P < 0.0001) (Table 2).

Table 1. Pain scores at 15 s after injection of 25% of the propofol dose.

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Severity of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No pain</td>
</tr>
<tr>
<td>Mild</td>
<td>Complaint of pain only when asked for</td>
</tr>
<tr>
<td>Moderate</td>
<td>Spontaneous complaint of pain</td>
</tr>
<tr>
<td>Severe</td>
<td>Spontaneous complaint of pain associated with grimacing or withdrawal of hand during injection</td>
</tr>
</tbody>
</table>

Table 2. Incidence of pain on injection with propofol.

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Saline (%)</th>
<th>Lidocaine (%)</th>
<th>Ketamine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>10 (20)</td>
<td>45 (90)</td>
<td>44 (88)</td>
</tr>
<tr>
<td>Mild</td>
<td>11 (22)</td>
<td>3 (6)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 (30)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (28)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total with pain</td>
<td>40 (80)</td>
<td>5 (10)&quot;</td>
<td>6 (12)&quot;**</td>
</tr>
</tbody>
</table>

Values are numbers (%). *P < 0.0001 compared with lidocaine group; **P > 0.05 compared with saline group.

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propofol in the same magnitude as lidocaine. The incidence of pain with lidocaine supported the findings of previous studies where a venous tourniquet was used. Previous investigators have found 20 mg lidocaine with a venous occlusion for 10, 20 or 30 s to be significantly better than placebo, suggesting that venous occlusion is important. Mangar and colleagues demonstrated that administering lidocaine after a tourniquet was inflated to 50 mmHg for 1 min virtually abolished the pain associated with propofol injection [4].

The tourniquet isolates the arm veins from the rest of the circulation and increases the action of locally acting substances. Tan and colleagues recently reported that the incidence of pain was significantly less (26%) with prior administration of ketamine 10 mg compared to a saline control group (86%) [2]. In a similar study, Suzuki and colleagues administered 1% ketamine (2 mL) prior to propofol and reduced the incidence of pain from 68% to 33% [5]. In none of these studies, venous retention was used. We found ketamine to be very effective in preventing propofol injection pain, especially moderate to severe pain in the presence of a venous tourniquet. Ketamine has analgesic properties that are mediated by a number of mechanisms. Ketamine in low doses is a potent non-competitive NMDA antagonist, and the analgesic action of ketamine is linked to an action at the NMDA receptor. Clements and Nimmo showed that the analgesic effect of ketamine occurs at much lower plasma concentrations (100 ng mL\(^{-1}\)) than the anesthetic effect (700 ng mL\(^{-1}\)) [6]. Ketamine resembles cocaine in chemical structure and shares some of its effects [7]. The results of this study suggest that ketamine modulates its effect at the peripheral site by a local mechanism as it has been reported to have local anaesthetic properties when given i.v. for regional anaesthesia. Durrani and colleagues reported that >0.3% ketamine (approximately 10\(^{-2}\) mol L\(^{-1}\)) produced adequate regional anaesthesia with complete sympathetic, sensory and motor block [8]. We used 2 mL of a 0.5% solution in our study. At this concentration, ketamine could produce analgesia and protect against propofol-induced pain. In conclusion, it is reasonable to consider i.v. ketamine with a tourniquet for 1 min as an effective alternative to lidocaine for reducing pain on injection with propofol.

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References

Influence of an external pacemaker on bispectral index

EDITOR:
Bispectral index monitoring is one technique to measure level of consciousness. The concurrent use of a variety of medical devices can lead to inaccuracies in its output. Among the recognized situations in which an external signal may interfere with it is an activated cardiac pacing device [1]. Usually, the

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A 72-yr-old man, New York Heart Association class II, with a myocardial infarction 4 months earlier, a history of controlled hypertension and mild diabetes mellitus presented for aortocoronary bypass grafting. Eighteen months before and due to inadequate medical control of repeated episodes of disrhythmias, a pacemaker (type DDD, model k™; Medtronic Inc., Minneapolis, MN, USA) with transvenous lead-electrode system had been implanted in the area near to his left clavicle. Preoperatively and in the operating room, 5-lead electrocardiography (Solar 8000; Marquette Medical Systems, Milwaukee, USA) revealed normal sinus rhythm without noticeable spikes. Following venous and arterial line placement and after skin preparation, a bispectral index sensor (BIS-XP®; Aspect Medical Systems, Newton, MA, USA) was placed which, when connected to the monitor showed a value of 98. After induction, the patient received continuous infusions of propofol (approximately 5 mg kg\(^{-1}\) h\(^{-1}\)) and remifentanil (approximately 20 \(\mu\)g kg\(^{-1}\) h\(^{-1}\)). Central venous access and mixed venous oximetry were established via the right internal jugular vein. After field preparation and a small incision, the implanted generator was disconnected and its transvenous electrode was connected to a stand-by single chamber external pacemaker (model: 5348; Medtronic Inc., Minneapolis, MN, USA). Normal sinus rhythm (55–65 beats min\(^{-1}\)) and bispectral index values ranging from 33 to 48 were recorded throughout the pre-bypass period. The patient’s body temperature was allowed to decrease passively during cardiopulmonary bypass while in the period near the completion of the main surgical procedure, before aortic unclamping and during the rest of bypass, active rewarming aided by the heart–lung machine was applied. In the 55 min of aortic clamping, bispectral index values were 23–44 and the lowest temperature recorded was 34.1°C. After removal of the aortic cross-clamp, the external pacemaker was connected to an epicardial electrode and set at 80 beats min\(^{-1}\) in asynchronous mode with output varying from 5 to 20 mA, in an effort to avoid loss of pacing capture. An increase in the bispectral index value to 69 was immediately noticed. The signal quality index was high. Changes in the pacemaker position, in order to increase the distance from the bispectral index sensor and digital signal converter did not affect the picture. Although the situation was suggestive of arousal, the attending anaesthesiologist noted that electromyographic activity was also high and proceeded to the evaluation of the real-time EEG. The rhythmic emission from the pacemaker was apparent, periodically interrupting the EEG and rarely followed by artefact recognition in the display. The bispectral index decreased to 45 shortly after the decrease in the output of the pacemaker and the displayed waves were also decreased in amplitude. Pacing was disconnected but the heart was still unresponsive and it was restarted under the lowest output for capture (10 mA). Bispectral index value showed marked variability ranging from 45 to 55, with no artefact detection but with high electromyogram intensity. Fifteen minutes later, pacing was discontinued as the patient established adequate sinus rhythm. Bispectral index values returned to around 40 and remained at that level. The remainder of the operation proceeded uneventfully and postoperative questioning elicited no evidence of recall.

Estimation of the current anaesthetic effect extends from the absolute bispectral index value to the assessment of the signal quality index, electromyogram and the real-time EEG. Activated pacemakers have been reported to interfere with bispectral index [2] but newer versions are supposed to recognize and eliminate such problems. Performance was quite acceptable in the beginning of pacing, when generator output was high. Nevertheless, the artefactual rise in signal could have been easily misinterpreted if the output had been low from the beginning. Brain temperature is expected to increase rapidly in the period of rewarming and its perfusion/mass ratio is high. Consequently cerebral metabolic rate is expected also to increase. A significant correlation has been found between bispectral index values and brain metabolic activity [3]. Although these changes were drug-induced, the pattern is suggestive of a similar relation between brain temperatures and bispectral index under a stable hypnotic drug blood concentration. A rise during rewarming and at the termination of bypass has been reported by many investigators [4–6]. In our case, this could obscure any moderate increase falsely arising from a pacemaker’s low current. During bispectral index monitoring, external interference remains a potential limitation and in similar situations it must be used in an appropriate manner. Observation of the real-time EEG waveform may aid in the diagnosis of this kind of artefact in order to avoid unnecessary interventions.

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References


Anaphylactic reaction after rocuronium

EDITOR:
Following the introduction of rocuronium bromide into clinical practice, several articles concerning allergic reactions have been published [1]. We would like to describe a life-threatening reaction after rocuronium followed by dysrhythmias, profound hypotension and stroke.

A 45-yr-old female was admitted for an elective gynaecological procedure because of cervical intraepithelial neoplasia (CIN 2–3). As a child she had a heart murmur but had never experienced cardiovascular problems. Preoperative physical examination, laboratory findings, electrocardiogram (ECG) and chest X-ray were all normal. She had never undergone surgery or anaesthesia before. Due to mild arthritis, she took occasional ibuprofen tablet. Neither she nor any member of her family had ever had an allergic reaction to food or drugs.

Two hours before surgery, she received dalteparine-sodium 0.3 mL subcutaneously followed by atropine 0.5 mg and midazolam 5 mg intramuscularly 30 min before surgery. An intravenous (i.v.) cannula was inserted in the operating room and routine monitoring applied.

Anaesthesia was induced with 15 mg of midazolam and 0.1 mg of fentanyl followed after 2 min by 40 mg of rocuronium bromide (a routine technique in our hospital). The patient was ventilated with 100% oxygen via a facemask. Immediately after injection of the rocuronium, systolic blood pressure (systolic BP) fell to 60 mmHg and heart rate (HR) to 100% oxygen via a facemask. Immediately after injection of the rocuronium, systolic blood pressure (systolic BP) fell to 60 mmHg and heart rate (HR) to 100% oxygen via a facemask. Immediately after injection of the rocuronium, systolic blood pressure (systolic BP) fell to 60 mmHg and heart rate (HR) to 100% oxygen via a facemask. Immediately after injection of the rocuronium, systolic blood pressure (systolic BP) fell to 60 mmHg and heart rate (HR) to 100% oxygen via a facemask. Immediately after injection of the rocuronium, systolic blood pressure (systolic BP) fell to 60 mmHg and heart rate (HR) to

An i.v. infusion of dobutamine was started and the BP gradually rose to a systolic BP of 60 mmHg. The atrial fibrillation was converted to sinus rhythm by verapamil 5 mg followed by a further 5 mg 10 min later. Tachydysrhythmias with occasional ventricular premature beats continued with a HR of 120 beats min\(^{-1}\).

The surgical procedure was postponed and the patient transferred to the intensive care unit. Her BP was now 145/85 mmHg with a HR of 120 beats min\(^{-1}\). The next day she had stable vital functions and the ECG was normal but neurological examination revealed a right-sided hemiplegia, head and neck deviation to the left side and aphasia. A stroke of the thalamic area was suspected although computed tomography and magnetic resonance imaging of the brain did not show any visible lesions. Doppler ultrasound scan of the brain vessels showed no localized stenosis. After neurological treatment and prolonged physical therapy the patient made a complete recovery.

Six months later, the patient underwent intradermal allergy testing to rocuronium, midazolam, fentanyl and placebo all at 1:20 dilutions. Rocuronium was positive, the rest were all negative. Cross-sensitivity tests to other muscle relaxants were not undertaken. Although the recommended time for skin testing is 6 weeks after the reaction, this was not possible due to circumstances beyond our control. Mast cell tryptase measurements were unfortunately not taken because the facility does not exist in our hospital to perform...
this measurement. Despite these limitations, we believe that this was an anaphylactic reaction to the rocuronium.

Anaphylactic reactions during anaesthesia are rare but may have dramatic and unpredictable consequences. Amongst the drugs used during anaesthesia, muscle relaxants have a high incidence of developing allergic reactions [2] with an incidence of 1 : 6500. Seventy percent of patients with a positive allergic reaction to one muscle relaxant show cross-sensitivity reactions to other muscle relaxants from that group [3]. It seems to be more common in females aged 20–40 yr. The mortality rate is about 3–4%. The mechanism behind anaphylactic reactions is immunologic and related to the formation of specific IgE antibodies. The usual technique for confirming allergy is the prick or intradermal test. The further use of muscle relaxants selected by negative intradermal tests has been proven to be safe [2]. Profound and prolonged hypotension is an uncommon side-effect of this group of drugs and has been attributed to ganglion blockade [4].

It is known that an anaphylactic reaction can develop in patients who have never undergone prior exposure to an agent. A possible explanation here might be the sensitization through the use of cosmetics and soaps which also contain the quaternary ammonium ion [5].

Following an allergic reaction, doctors must fully inform their patients about the situation [5]. Tests including all drugs to which the patient was exposed should be obtained 4–8 weeks after the incident occurred with particular attention to cross-sensitivity [6]. Investigations should be performed to confirm the nature of the reaction if possible, which of the suspected drugs were responsible and to provide recommendations to the patient for future anaesthetic procedures. All side-effects should be recorded. Contacts with colleagues and reports to National centres for adverse reactions must also become a part of routine practice.

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References

Complete recovery from prolonged cardiac arrest following self-administration of cisatracurium

EDITOR:
We report a case of prolonged cardiac arrest with complete recovery following accidental intravenous (i.v.) self-administration of cisatracurium.

A 46-yr-old, 155 cm, 90 kg female, with a past medical history of asthma and drug allergies, suffered from recurrent headaches. By mistake, instead of an analgesic drug (Nimedex – nimesulide), a neuromuscular blocking drug with a similar name (Nimbex – cisatracurium) was self-administered by i.v. bolus. She had taken no other drugs. Muscular paralysis resulted in cessation of respiration and subsequent cardiac arrest. A physician attended and electrocardiogram (ECG) confirmed the absence of cardiac electrical activity. It was thought that the patient had irreversibly died and resuscitation was not attempted by bystanders. From the time of documented cardiac...
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220/120 mmHg and heart rate 140 beats min

sure haemodynamic parameters was seen with arterial pres-

sure and atropine 2 mg had been used, ECG activity
cardiac electric activity during which epinephrine

Correspondence

tive efforts exceeded 30 min after cardiac arrest

Studies on CPR quote no survivors when resuscita-
tion of resuscitation and survival after cardiac arrest.
The following 18 months and no abnormalities were

days after the cardiac arrest and 6 weeks later but they

brain magnetic resonance imaging was performed 2

to possible delayed post-hypoxic encephalopathy,

removed. She made a full recovery and was discharged

tors Glasgow coma score was 15, the patient was

impairment is seen more often in patients with

obesity. Resuscitation included epinephrine, atropine

and sodium bicarbonate. Drugs with potential neuro-

protective properties were not administered. Due

to the prolonged duration of ischaemia, the prognosis

was expected to be poor. The patient not only sur-
vived such a prolonged life-threatening event, how-

ever, but also went on to exhibit full neurological

recovery.

The patient had self-administered cisatracurium. Laudanosine, a major metabolic degradation product of cisatracurium, crosses the blood–brain barrier and accumulates in cerebrospinal fluid [3]. Laudanosine, at concentrations comparable to those measured under clinical conditions in cerebrospinal fluid is able to activate \( \alpha_{1}\beta_{2} \)-nicotinic acetylcholine receptors [3]. These receptors are present throughout the nervous system and are involved in chemical signalling. Several studies have suggested that \( \alpha_{1}\beta_{2} \)-nicotinic acetylcholine receptor activation elicits a neuroprotective effect, \textit{in vivo} and \textit{in vitro} [4]. Therefore, it has been hypothesized that laudanosine, at clinical concentrations reported, could exhibit potential neuroprotective effects [5]. This hypothesis is further supported by the fact that in concentrations seen clinically in blood and approaching those measured in cerebrospinal fluid, laudanosine interacts with \( \delta \)- and \( \kappa \)-opioid receptors, activation of which may also result in neuroprotection against hypoxia and ischaemia [3,5].

In addition to the above, the rapid return of haemodynamic stability merits consideration. Global left ventricular dysfunction after successful resuscitation is well documented and appears to be a major contributing factor in limiting long-term survival after initial recovery [6]. Nevertheless, after prolonged cardiac arrest and CPR, our patient exhibited an almost immediate and impressive haemodynamic stability following restoration of cardiac activity. After prolonged cardiac arrest, the direct activation of nicotinic receptors in the central nervous system
has been associated, in animal studies, with an immediate and impressive increase in mean arterial pressure and heart rate, with normalization of ECG within a few minutes [7]. It is tempting to speculate that activation of central nicotinic receptors [4] by laudanosine may have helped. It could not have been the neostigmine [7] as this was administered only after subsequent admission to intensive care.

We do realise that what has been reported above is very tenuous but, taken together, it seems that there could be a potential role for laudanosine in neuro-protection and cardioprotection.

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References

A clinical comparison between bispectral index (BIS) and high frequency EEG signal detection (SNAP)

EDITOR:

General anaesthesia is a complex condition which includes several different components such as muscular relaxation, analgesia, amnesia and hypnosis. Electroencephalographic changes appear to correlate with drug concentrations at the effect site and a number of different indices have been developed in an attempt to identify an objective way of monitoring the depth of anaesthesia. Bispectral index (BIS) integrates several disparate descriptors of the electroencephalogram (EEG) into a linear scale from 0 to 100 and this has been reported to correlate with clinical end-points of the hypnotic state [1]. Evidence is accumulating that BIS monitoring can help in assessing the hypnotic component of anaesthesia, reduce drug consumption and shorten recovery times as compared to a standard anaesthesia protocol [2,3].

More recently another monitoring system which uses EEG signal detection has become commercially available in Europe, the ‘SNAP’ EEG monitor (Nicoleo Biomedical, Madison, WI, USA). This monitor samples raw EEG signals and, using its own unique algorithm, analyses both the low (0–20 Hz) and high (80–420 Hz) frequency components of the signal to produce a derived measurement. This is termed the ‘SNAP Index’ and ranges from 0 to 100 (with 100 arbitrarily representing the fully awake state). Before introducing any new anaesthesia index into daily practice, more information on the correlation with already available technology is needed. We, therefore, conducted a prospective study to evaluate the relationship between the SNAP and the BIS indices during general anaesthesia.

With Ethical Committee approval and written informed consent, 10 females undergoing outpatient gynaecological procedures of maximum 1 h duration were prospectively studied. Their mean (±SD) age was 47 ± 8 yr, height 167 ± 5 cm and weight 57 ± 8 kg. All patients were premedicated with intravenous (i.v.) midazolam (0.03 mg kg⁻¹). The skin of the forehead was degreased with isopropanol 70% and both BIS and SNAP electrodes (BIS Sensors™, Aspect Medical System, Newton, USA and SNAP Sensors™, Nicoleo Biomedical, Madison, WI, USA, respectively) were applied as recommended by the manufacturers. Impedance testing was performed according to the manufacturers’ instructions before starting the study in each patient to be sure that electrode contact was optimal.

A remifentanil infusion at 0.25 µg kg⁻¹ min⁻¹ was commenced and 5 min later propofol was given to induce general anaesthesia using a target-controlled infusion (Diprifusor, Astrazeneca, Italy) with an initial set target plasma concentration of 4 µg mL⁻¹. After loss of consciousness oxygen was given by face
mask ventilation. When adequate relaxation of the jaw was observed a laryngeal mask was placed and secured to allow safe airway control and the lungs mechanically ventilated to maintain an end-tidal carbon dioxide concentration ranging between 32 and 36 mmHg. After laryngeal mask placement the remifentanil infusion was reduced to between 0.01 and 0.02 µg kg\(^{-1}\) min\(^{-1}\) to maintain cardiovascular stability (systolic arterial pressure values within ±20% from baseline values). The propofol plasma target concentration was adjusted to between 3.5 and 2.5 µg mL\(^{-1}\) to maintain an adequate level of hypnosis. Before the expected end of the surgical procedure the propofol target was reduced to facilitate rapid emergence from anaesthesia. The remifentanil infusion was stopped at the end of surgery. When adequate recovery of spontaneous breathing and swallowing was reached, the laryngeal mask was removed. An independent observer not involved in patient care recorded both BIS and SNAP values every 1 min throughout the procedure until emergence and laryngeal mask removal.

Statistical analysis was performed using the statistical software package Systat 7.0 for windows (SPSS Abacus Conc, USA). A correlation analysis with linear regression analysis was first performed between the SNAP and BIS indices then the agreement between the two indices was assessed using the Bland–Altman method [4].

A total of 446 pairs of data were obtained. A significant correlation was observed between SNAP and BIS indices (r = 0.15; P < 0.01). The Bland–Altman analysis (Fig. 1) demonstrated a positive bias of about 10 points of the SNAP index as compared to the BIS index (95% confidence intervals: −31 to +51).

The BIS scale has been demonstrated to correlate with anaesthetic concentrations of several drugs, such as midazolam, propofol and volatile anaesthetics [2,3,5,6]. The use of depth of anaesthesia monitoring to reduce the incidence of intraoperative awareness is still questionable and difficult to study [7], although titrating anaesthetic drugs with the guide of the BIS index may hasten the recovery from anaesthesia with resultant reduction in the total dose of anaesthetic drugs required to maintain general anaesthesia. Like the BIS value the SNAP index is also derived from EEG recording using a unique algorithm that produces a numeric index. Interestingly, the software making the calculations is placed on a small handheld computer. The SNAP index is updated at 1 s intervals from a 15-point moving average of the ratio of weighted high and low frequency components from a single channel digitized EEG signal. Before using this new system in our routine practice, comparative data against the accepted standard monitoring of the level of hypnosis were required. Although results of this prospective study demonstrated significant correlation between SNAP and BIS indices, the correlation was not very high. The SNAP index tended to read approximately 10 points higher than the BIS value and this overestimation may need to be taken into account. All of the patients in this study were female, and it is possible that gender may also be a relevant factor [6]. Further prospective investigations are clearly needed to better evaluate the effects of different concentrations of i.v. and inhalational anaesthetics on the SNAP index.

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The laryngeal mask airway (LMA™) in paediatric ophthalmic anaesthesia practice

EDITOR:
Many ophthalmic procedures in children require general anaesthesia. In appropriate patients the laryngeal mask airway (LMA) is an acceptable technique for intraocular surgery, offering advantages in terms of intraocular pressure and cardiovascular stability when compared with tracheal intubation. The principal disadvantage is that the airway may be compromised unexpectedly during the procedure. The aim of this study was to assess the use of the LMA in infants and children undergoing both intraocular and extraocular elective ophthalmic surgery.

The first choice of airway management for procedures under general anaesthesia was the LMA in each patient, except for patients at risk of aspiration. The first two authors were experienced in using the LMA in children. All patients, except those ≤ 6 months of age were premedicated orally or rectally (according to the age of the patient) using midazolam 0.5 mg kg⁻¹ approximately 30 min before the planned operation (maximum dose 15 mg). Induction was performed using sevoflurane 8% in N₂O 50% with oxygen by facemask or propofol 3–4 mg kg⁻¹ when intravenous (i.v.) access could be obtained. The LMA up to size 3.0 was inserted in a manner similar to using a Guedel oropharyngeal airway (inserting the deflated mask with its lumen facing backwards and then rotating through 180° as it passes downwards into position behind the larynx). Other sizes were inserted in the standard way described by Brain. When the LMA could not be inserted in spite of multiple attempts, tracheal intubation was performed and this was documented on the anaesthesia record. Patients undergoing intraocular surgery or procedures expected to last longer than 30 min received a non-depolarizing muscle relaxant before the insertion of the LMA. These patients were ventilated mechanically. When i.v. induction could be obtained, anaesthesia was maintained with propofol and remifentanil. In other patients anaesthesia was maintained with 2.0–3.0% sevoflurane in 50% N₂O and oxygen. Acetaminophen 40 mg kg⁻¹ (or diclofenac 1.0 mg kg⁻¹ for older children) was administered rectally after induction to all patients except those who underwent only ocular examination under general anaesthesia. Routine antiemetic prophylactic drug therapy (metoclopramide 0.2 mg kg⁻¹) was used for strabismus surgery. The LMA was removed at the end of surgery during deep anaesthesia and replaced with a Guedel airway in all children. Jaw lift and face-mask were applied with 100% oxygen after removal of the LMA.

The LMA was successfully used in 141 patients. The median weight was 16.0 kg (range 3.5–75 kg). The mean duration of the operation was 58 min (range 10–180 min), and the male:female ratio was 69:72. Distribution according to age groups and LMA size is shown in Table 1. Intravenous anaesthesia was administered to 28.4% of the patients and 71.6% received inhalational anaesthesia. Muscle relaxation was used in 65.2% of patients. There were a total of 10 critical incidents, of which one was related to the airway and the others to the oculocardiac reflex. Bradycardia developed in nine patients undergoing strabismus surgery. The surgeon was immediately informed, surgery temporarily halted and atropine 10 µg kg⁻¹ was given. One infant (1 month of age,
Table 1. Age groups and size of the LMA.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Number of patients (%) (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>26 (18)</td>
</tr>
<tr>
<td>2–4</td>
<td>53 (38)</td>
</tr>
<tr>
<td>5–10</td>
<td>49 (35)</td>
</tr>
<tr>
<td>11–17</td>
<td>13 (9)</td>
</tr>
<tr>
<td>LMA size (according to weight)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>4 (3)</td>
</tr>
<tr>
<td>1.5</td>
<td>27 (19)</td>
</tr>
<tr>
<td>2.0</td>
<td>58 (41)</td>
</tr>
<tr>
<td>2.5</td>
<td>38 (27)</td>
</tr>
<tr>
<td>3.0</td>
<td>11 (8)</td>
</tr>
<tr>
<td>4.0</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

congenital cataract surgery) developed desaturation to $S_{p}O_{2} < 90\%$ after removal of the LMA which was treated with gentle positive pressure ventilation using 100\% oxygen. No intraoperative displacement of the LMA occurred in any of the patients.

The LMA is a relatively non-invasive airway compared with the tracheal tube, and clinical data suggest that laryngospasm, bronchospasm and coughing occur less frequently than with the tracheal tube. Watcha and colleagues [1] compared the effects of LMA and endotracheal tube insertion on intraocular pressure in children and concluded that the laryngeal mask offers advantages for airway management in patients undergoing intraocular pressure measurements. In that study, children <9 month of age and <5 kg body weight were excluded and there is no information concerning difficulties in inserting the LMA or its size. Ateş and colleagues [2] investigated airway complications related to LMA use in paediatric patients undergoing ophthalmic surgery. Their successful insertion rate at the first attempt was 93\%. In our study the LMA could be inserted in all patients. This very high success rate may be due to our routine insertion technique and to the use of all sizes of the LMA including the size 1.5. It has been suggested that insertion of the laryngeal mask airway in a manner similar to a Guedel airway may be successful when difficulty is encountered with the conventional technique described by Brain. Nakayama and colleagues [3] compared the rotational technique using a partially inflated laryngeal mask airway and the standard ‘non-rotational’ technique with a result of successful insertion on the first attempt in 99\% of patients in the rotational group compared to 79\% in the other group. We usually insert the LMA up to size 3.0 using the rotational method and we have a high success rate in inserting LMA without partial inflation. Lopez-Gil and colleagues [4] reported a decrease in complications with increase in skill of the anaesthetist. In our routine practice the LMA in infants is inserted and removed by experienced anaesthetists and this may be another factor for our success rate. One patient in our study showed decrease in $S_{p}O_{2}$ at the end of surgery and developed desaturation to a value of 84\% $S_{p}O_{2}$ after removal of the LMA size 1.0. It has been shown that obstruction tends to be more frequent with the size 1 LMA and impinging of the epiglottis in the LMA bars is nearly twice as frequent with the size 1 LMA when compared with size 2 LMA [5]. The timing of removal of the LMA may also have an effect on respiratory complications. Brain and others recommend removal of the LMA when protective upper airway reflexes have returned. Kitching and colleagues [6] found that LMA removal during deep anaesthesia could decrease the incidence of coughing, laryngospasm, desaturation, excess salivation, biting, retching, vomiting and airway obstruction during the emergence. Upper airway reflexes are of primary importance to anaesthesia. Their activation during anaesthesia can lead to apnoea and laryngospasm which, besides being a minor inconvenience, may also be life threatening. Therefore, adequate suppression of airway reflexes is necessary for safe anaesthesia. We removed the LMA in deeply anaesthetized patients to prevent coughing.

Besides induction and emergence, maintenance of anaesthesia in ophthalmic surgery is also important. The use of muscle relaxants in eye surgery allows maintenance of a lighter level of anaesthesia without the risk of movement of the patient. Therefore we used non-depolarizing muscle relaxants according to type of surgery or duration even though it was not necessary for insertion of the LMA. Inadequate anaesthesia or inadequate relaxation (pharyngeal muscle and/or laryngeal spasm) is also a common cause of poor LMA placement and management [3,7].

There was no documented airway compromise during surgery in any patient and no complication during insertion and removal of the LMA in our patients. We conclude that the laryngeal mask airway can be safely and effectively used in ophthalmic surgery when optimal insertion and extubation conditions are provided.

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