Neuraxial blockade and patient risk

EDITORS:
I was interested to read both an editorial and an article relating to the risk of neuraxial blockade in one issue of the European Journal of Anaesthesiology [1,2]. Whilst I wholeheartedly agree with the arguments and sentiments expressed in Kamming and Davies’ editorial, I am afraid I cannot agree with Bogdanov and Loveland. I would suggest that it does not require a double-blind trial to recognize that the likelihood of, especially neural, damage is greater whilst needles are being inserted into an anaesthetized patient rather than one from whom immediate feedback is available.

Using the method described by Ho to estimate the incidence of rare adverse events that have not (yet) occurred [3], we can estimate with 95% confidence that the maximum risk of damage detectable by a surgeon in outpatients following brachial plexus block under general anaesthesia for shoulder surgery using Bogdanov and Loveland’s technique is 3 in 548 or 1:183. Hopefully, the risk to the patient is in reality, much less than this, but it does go to show how little help a small series such as this is in weighing the ‘before induction or after induction’ argument.

I would argue that it is impossible to state to the patient that it is safer to have the brachial plexus block placed after induction of anaesthesia and that the difference in risk is difficult to quantify; but it must exist.

Since the dismissal by the Lords of the appeal against the Chester vs. Afshar ruling [4] it is now abundantly clear that we have a duty to explain all the risks to the patient and allow the patient to make the decision as to which technique is used. This does not mean that Bogdanov and Loveland should not continue to do what they do, but more that the patient must choose to have the block put in asleep after the risks, as we know them, have been fully explained.

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References

EDITOR:
The report by Bogdanov and colleagues [1] of complication-free interscalene brachial plexus blockade performed in 548 patients under general anaesthesia should not support the common use of this practice. Although the authors highlight the absence of cervical spinal cord damage during block administration, we feel that the more relevant complications of interscalene block regarding its practice in awake vs. asleep patients are intravascular and intraneural injection. Moreover, estimating the incidence of rare events from small sample sizes is a well-known problem in clinical research, and is all the more salient when those rare events may be catastrophic. Furthermore, what may be safe and reasonable practice in the hands of the expert may not apply to the practice of someone still progressing on the learning curve or the student.

In a study by Borgeat and colleagues, the overall rate of complications following interscalene block was found to be 0.4% [2]; however, the exact frequency of intravascular and intraneural injection during interscalene block is unknown. Benumof has reported on cases of permanent loss of neurological function following brachial plexus blocks performed under general anaesthesia or heavy sedation [5]. Intravascular injection...
can lead to local anaesthetic toxicity, including seizures and cardiac arrest. Intraneural injection may lead to permanent sensory and motor deficits [4]. These complications should be easier to avoid in an awake patient.

It is widely believed that the most sensitive indicator of intraneural injection of local anaesthetic is severe pain and a withdrawal reaction immediately upon injection. This response cannot be assessed in the deeply sedated patient or the patient under general anaesthesia. Although both an increased resistance to injection and the persistence of a motor response at a stimulating current of less than 0.2 mA are suggested indicators of potential intraneural injection [5,6], they are not reliable. Similarly, intravascular injection can be caught early and terminated by acting on information only available through an awake, communicating patient. Soliciting feedback on the presence or absence of early warning signs of systemic toxicity such as tinnitus, perioral numbness or subtle changes in mental status allows one to stop the injection short of seizure and/or cardiovascular collapse. Furthermore, aspiration alone may not adequately protect against intravascular needle placement; despite immobile needle techniques, small movements in needle position may lead to transient intravascular placement and over-vigorous aspiration may result in collapse of the vein wall against the needle aperture resulting in a ball-valve effect and inability to aspirate blood. Hadzic and Vloka have also postulated intravascular ‘channelling’ of local anaesthetic under high injection pressures into blood vessels and lymphatics traumatized during needle placement [6].

In our opinion, the importance of patient feedback to the safe application of the interscalene brachial plexus block has been underestimated, particularly in the case of the nonexpert. Although the experience of Bogdanov and colleagues was complication-free, a series of 548 patients is inadequate to define the incidence of rare complications compared to that incidence in an awake patient population. As the outcome of these rare complications has the potential to be catastrophic, we feel the standard of practice for the performance of an interscalene block should incorporate all measures which can minimize risk, including maintaining communication with the patient.

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References


Reply

EDITOR:

We appreciate the interest of Dr Hunter and of Drs Egan and Brown in our study [1] and thank them for their comments. This area of regional anaesthesia, and especially those aspects relating to safety, remains controversial. As far as we are aware, there are no studies published that establish that an ‘awake’ approach confers additional safety over an ‘asleep’ one.

In the absence of Class 1 evidence, we agree with the opinion of Fisher [2]. In addition, we would like to quote an extract from a lecture by Professor Boezaart [3], an acknowledged expert on the subject of regional anaesthesia and interscalene block in particular:

Intraneural injection of a local anaesthetic is not painful and we should probably not be fooled by the false security that doing blocks in nonanaesthetized patients would protect us from intraneural injection. The real ‘horror stories’ of pain associated with intraneural injection come from the radiology literature where contrast medium and not local anaesthetic agent is injected.

Secondly, injection of local anaesthetic agent next to a nerve in a confined space, e.g. the intervertebral foramen, can cause the excruciating pain referred to by some. Another example would be the ulnar nerve at the elbow. In 2000, Benumof [4] reported 4 cases of permanent loss of cervical cord function associated with interscalene block performed under general anaesthesia.

From these cases, but also from numerous other case reports, it was concluded that doing blocks on patients who are not under general anaesthesia or heavily sedated protects from intraneural injection and subsequently against nerve damage. Nobody looked at the technique used and the direction of the needles. And people do not seem to realize
that the injection of local anaesthetic agent near (or even inside) a nerve immediately ends all motor function of that nerve. So why would the motor function be blocked immediately but the sensory function be spared? And can we rely on pain to protect us from doing intraneural injections? I think not!

Horlocker and colleagues [5] looked at more than 4000 lumbar epidurals inserted after induction of general anaesthesia and concluded that ‘... although the risk of neurological complications associated with lumbar epidural catheter placement in anaesthetised patients is small, the relative risk compared with epidural catheterisation in awake patients is unknown’.

Therefore, the subject is controversial and opinions are divided. In our article we presented the data showing that in our series, interscalene block performed in anaesthetized patients is safe. To prove whether it is safer than an ‘awake’ technique was not the aim of our study and as far as we are aware there are no studies on that subject. We of course agree with the good practice implicit in informing patients fully of all pertinent choices and their attendant risks. However, we would strongly disagree with the statement that ‘it does not require a double-blind trial to recognise that the likelihood of, especially neural, damage is greater whilst needles are being inserted into an anaesthetised patient rather than one from whom immediate feedback is available’. This statement would seem to be based upon opinion alone.

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References

General anaesthesia for a super obese patient

EDITOR:
Due to the difficulty in enrolling a large number of super obese patients (body mass index, BMI > 50 kg m$^{-2}$) the anaesthetic management of these patients is still inferred from evidence based on obese or morbidly obese patients [1]. We report a case of a 35-year-old 220-kg male, ASA III, scheduled for laparotomy with Roux-en-Y gastric bypass. His height was 172 cm, BMI 74.7 kg m$^{-2}$, with an ideal body weight of 74 kg. Thus his real body weight was 298% of his ideal weight with a weight excess of 147 kg. Anaesthesiology evaluation 12 days prior to surgery revealed: hypertension (160/90 mmHg), oesophagitis (primary grade, Savary classification), mild hyperuricaemia, hyperinsulinaemia and increased hepatic enzymes. Abdominal echography was normal as well as electrocardiogram and spirometry. Given the neck circumference of 52 cm and Mallampati class III airway, awake intubation was discussed and planned with the patient, who appeared motivated regardless of the possible discomfort of the procedure.

The day before surgery, omeprazole 20 mg was commenced twice a day orally and crystalloids 2000 mL overnight were administered. Omeprazole 40 mg was given intravenously (i.v.) 1 h prior to arrival in the operating room. Following standard monitoring, the left radial artery was cannulated. The patient tolerated well the awake autocalibration of neuromuscular function monitoring train-of-four (TOF-Watch). Midazolam 0.05 mg kg$^{-1}$ (based on ideal body weight) was then administered. Following topical anaesthesia, awake fibreoptic endotracheal intubation was performed. The epiglottis appeared small and moderately hypertrophic. Immediately

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after placing the endotracheal tube, anaesthesia was induced with propofol 2.5 mg kg\(^{-1}\) and rocuronium 0.6 mg kg\(^{-1}\) based on ideal body weight. A remifentanil infusion was begun at 0.45 µg kg\(^{-1}\) min\(^{-1}\) again based on ideal body weight. Volume-controlled mechanical ventilation was set at a respiratory rate of 12 breaths min\(^{-1}\) and a tidal volume of 10 mL kg\(^{-1}\) ideal body weight, with F\(_{O_2}\) of 0.5 and PEEP of 5 cmH\(_2\)O. It was modified thereafter to maintain an end-tidal CO\(_2\) of 35–40 mmHg. Anaesthesia was maintained with desflurane and remifentanil. Desflurane was titrated on bispectral index (BIS) values whereas the remifentanil infusion was titrated against haemodynamic monitoring.

Neuromuscular transmission was monitored by the response to single twitch stimuli at 0.1 Hz, using acceleromyography of the adductor pollicis muscle (TOF-Watch; Organon Technica, BV, NL). The onset time of 0.6 mg kg\(^{-1}\) of rocuronium was 88 s and duration of action (recovery to 25% of control) was 27 min. Recovery was monitored by TOF stimulation. Additional doses of rocuronium were administered as requested, based on neuromuscular monitoring. BIS was maintained between 40 and 60 (BIS monitor Model A 2000; Aspect Medical System Inc., Newton, MA, USA). End-tidal fraction of desflurane varied during maintenance of anaesthesia, between 4.0% and 5.7%.

Non-invasive haemodynamic monitoring was performed by the HemoSonic (HemoSonic\textsuperscript{®} 100; Arrow International, Everett, MA, USA) transesophageal echo-Doppler. Remifentanil infusion varied between 0.11 and 0.51 µg kg\(^{-1}\) min\(^{-1}\) with considerable intraoperative haemodynamic stability: mean arterial pressure (MAP) 69 ± 5 mmHg, heart rate (HR) 84 ± 12 min\(^{-1}\), aortic blood flow 9.0–11.5 L min\(^{-1}\), stroke volume 84–156 mL beat\(^{-1}\), acceleration 15.1–20.6 m s\(^{-1}\) and total systemic vascular resistance 793–1106 dyn s cm\(^{-5}\).

Repeated arterial blood gas sampling was performed to confirm adequacy of ventilation during anaesthesia, prior to and after extubation, as well as in the recovery room. The surgical procedure lasted 6 h. Approximately 30 min before stopping the infusion of remifentanil, ketorolac, 30 mg, was administered i.v. Surgical wound infiltration with bupivacaine 0.25% (40 mL) was performed. Reversal of neuromuscular blockade by neostigmine 0.05 mg kg\(^{-1}\) and atropine 0.02 mg kg\(^{-1}\) both based on ideal body weight was undertaken 15 min before extubation, the TOF ratio being 0.55. Extubation was safely performed 7.5 min after interrupting desflurane administration. BIS values rose rapidly from 42 before interrupting desflurane administration to 64 after 4 min and to 88 3 min later. 30 s thereafter, the value was 94 and the patient was extubated. Extubation was performed under fibreoptic vision with a TOF ratio of 0.9. Meperidine 30 mg was administered 15 min after extubation. The patient was transferred under strict monitoring to the recovery room with an arterial pressure of 140/80 and a S\(_{O_2}\) of 100 with a P\(_{F_2O_2}\) of 0.5.

Postoperative pain was managed by an i.v. infusion of tramadol, 200 mg, and ketorolac, 60 mg, over 24 h. Recovery was uneventful and pain, graded by visual analogic scale, ranged between 0 and 2. Face mask oxygen therapy was continued overnight. No desaturation episodes (S\(_{O_2}\) < 90) were recorded overnight and no further analgesia was required. When questioned on days 2 and 8, the patient did not remember the fibreoptic awake intubation but only topical anaesthesia of the pharynx. Amnesia included extubation since the first memories dated to the recovery room. No complications were observed and the patient was discharged on the 8th postoperative day.

In the present case, we coupled the use of short-acting agents such as desflurane, remifentanil and rocuronium with continuous intraoperative monitoring of their effects. Desflurane was titrated on BIS values, rocuronium was administered on the basis of twitch response and remifentanil infusion was adjusted on haemodynamic monitoring documented by transesophageal echo-Doppler and blood pressure.

Morbid obesity is responsible for several pharmacological changes including alterations in the distribution, binding and elimination of many drugs. Hence, the resulting pharmacodynamic effect is often unpredictable and uncertain, making drug titration even more difficult [2]. Desflurane, owing to its low solubility, is rapidly released from tissues and eliminated at the end of prolonged anaesthesia. Consequently, morbidly obese patients experience a significantly faster immediate recovery when receiving desflurane-remifentanil anaesthesia compared to sevoflurane-remifentanil [3]. Remifentanil’s ester structure accounts for its rapid metabolism by blood and tissue esterases to inactive products independent of renal and hepatic function. Moreover, remifentanil pharmacokinetics are not appreciably different in the obese and therefore remifentanil dosing regimens should be based on ideal body weight [4]. Muscle relaxants with weak or moderate lipophilicity such as rocuronium are distributed mainly in lean tissue. Accordingly, the dosage of rocuronium in obese patients should be based on ideal rather than on real body weight [5].

Recently Gaszynski and colleagues [6] reported a case of intraoperative management of a super obese patient (219 kg, BMI 70.7). Induction with remifentanil, midazolam and propofol, was followed by midazolam and a mixture of 66% nitrous oxide in oxygen for maintenance of anaesthesia. Cisatracurium was
used to facilitate oral endotracheal intubation. We preferred rocuronium because of its shorter onset and duration of action in morbidly obese, awake fiberoptic intubation and a low-solubility hypnotic volatile agent such as desflurane for maintenance of anaesthesia [7]. For intraoperative analgesia we utilized remifentanil at an infusion rate between 0.11 and 0.51 µg kg$^{-1}$ min$^{-1}$ in contrast with the range of 0.5–0.75 µg kg$^{-1}$ min$^{-1}$ reported by Gaszynski and colleagues [6].

In conclusion, we report the use of short acting drugs coupled with intraoperative monitoring of the effects of each agent. Such strategy resulted in considerable intraoperative stability and prompt recovery of respiratory function allowing rapid extubation in the operating theatre and uneventful recovery.

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**References**


**Intraperitoneal tramadol and bupivacaine in total abdominal hysterectomy**

**EDITOR:**

Postoperative pain is a major postoperative problem. The use of intraperitoneal local anesthetic agents has been shown to reduce postoperative pain [1]. In contrast, other investigators have found that intraperitoneal administration of either bupivacaine or morphine was not effective in reducing postoperative pain [2]. Tramadol has a dual mechanism of action where it blocks the reuptake of norepinephrine and 5-hydroxytryptamine at the α2 adrenergic receptor level [3]. The aim of this study was to examine the intraperitoneal application of saline, bupivacaine and bupivacaine with tramadol and compare it with intravenous (i.v.) tramadol on postoperative pain following total abdominal hysterectomy.

Following Ethics Committee approval and written informed consent, 100 patients were randomly divided into four groups. The first three received 20 mL saline (Group S), bupivacaine 0.5% 20 mL (Group B) or bupivacaine 0.5% 20 mL with tramadol 100 mg (Group BT) administered into the peritoneal cavity. The fourth group received 100 mg tramadol i.v. (Group T). Postoperative pain was evaluated using a visual analog scale (VAS) at 30 min and at 2, 4, 6, 12, 18 and 24 h after extubation. Mean arterial pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO2) were also noted. When pain scores were between 3 and 6, 0.5 mg kg$^{-1}$ pethidine (meperidine) was given intramuscularly (i.m.) as a rescue analgesic. If the pain score was >6, 1 mg kg$^{-1}$ meperidine was given. The rescue analgesic dose, time and side-effects were noted.

No significant differences were found in demographic criteria and SpO2. When Groups S and B were compared with Groups BT and T at 30 min, 2 and 4 h, MAP and HR were found to be significantly greater ($P < 0.001$). Pain scores in Groups S and B were significantly higher when compared with Groups BT and T at 30 min ($P < 0.001$), 2 ($P < 0.001$) and 4 h ($P < 0.05$). When Groups BT and T were compared, no significant differences were found (Table 1).
Recombinant activated factor VII to control massive postoperative bleeding after septic aortobifemoral grafting

EDITOR:
Recombinant activated factor VII (rFVIIa, NovoSeven®, Novo Nordisk, Copenhagen, Denmark) is mainly used as a pro-haemostatic agent for the treatment of haemophiliac patients with inhibitors [1].

However, it has also proven its clinical effectiveness in patients with Glanzmann thrombasthenaemia and thrombocytopaenia [1]. Moreover, rFVIIa has been recently used in patients without pre-existing coagulopathy to control perioperative bleeding in various clinical situations such as trauma [2], cardiac surgery, vascular surgery, hepatectomy, gynaecological surgery or left ventricular assistance.

A 56-yr-old man with a prior history of two aortobifemoral grafts for acute abdominal aortic thrombosis, complicated by postoperative acute severe pancreatitis, developed a prosthetoenteric fistula has been demonstrated that local intraperitoneal bupivacaine and intraperitoneal meperidine were better than the combination of intraperitoneal bupivacaine and i.m. meperidine for postoperative analgesia in patients undergoing laparoscopic tubal ligation demonstrating a local effect [5]. In our study, we found that tramadol when added to intraperitoneal bupivacaine was as effective in the early postoperative period as i.v. tramadol.

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References

Table 1. Postoperative pain scores measured on a 10 cm VAS.

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<td>30 min</td>
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<td>8 (6–10)</td>
<td>5 (2–8)‡</td>
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<td>2 h</td>
<td>8 (6–10)</td>
<td>7 (4–9)</td>
<td>5 (2–6)‡</td>
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<td>4 h</td>
<td>5 (1–8)</td>
<td>5 (1–6)</td>
<td>4 (2–5)‡</td>
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<td>6 h</td>
<td>4 (1–6)</td>
<td>4 (1–5)</td>
<td>3 (2–4)</td>
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<td>12 h</td>
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<td>24 h</td>
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*P < 0.001 when compared with Groups S and B; †P < 0.05 when compared with Groups S and B. Data are expressed as median (range).
7 months after an episode of cholangitis and was scheduled for emergency venous autograft replacement. He was treated receiving aspirin and clopidogrel which could not be withdrawn because of the emergency conditions. He had normal platelet count and coagulation screen at the time of admission.

The Dacron graft was exposed through a left thoraco-phreno-laparotomy. Surrounding pus was sampled for bacteriological analysis. The graft was completely removed under supra-coeliac aortic cross-clamping and replaced by a bifurcated aortograft fashioned with both superficial femoral veins. An aortic tear occurred during aortic control because of sudden arterial hypertension, requiring a 4 cm thoracic aortic Dacron graft replacement. Aortic clamp time was 25 min at the supra-coeliac level and 50 min at the supra-renal level. During reperfusion, non-surgical bleeding developed requiring administration of 27 units of red blood cells, 10 units of platelets, 18 units of fresh frozen plasma and aprotinin (2 million kallikrein inhibiting units).

The immediate postoperative period in the intensive care unit (ICU) was marked by continuous bleeding (>1800 mL h$^{-1}$) through two of the drains and acute haemostasis disorders were observed (prothrombin ratio 20%, fibrinogen 0.7 g L$^{-1}$, platelets count $32 \times 10^{9}$ L$^{-1}$, activated partial thromboplastin ratio 5.5). Despite administration of 18 units of blood, 24 units of fresh frozen plasma, 21 units of platelets, 3 g of fibrinogen, continuation of intravenous (i.v.) aprotinin administration and the absence of hypothermia (35.5°C), bleeding was still active and justified a second surgical look 5 h later. Active bleeding from a diaphragmatic vein, a pulmonary wound and the lower aortic graft anastomosis were surgically corrected. Perioperative blood loss required massive transfusion (13 units of blood, 12 units of fresh frozen plasma and 10 units of platelets).

In the second postoperative period, the patient remained unstable justifying continuous haemodynamic support with norepinephrine, continuation of antiplatelet therapies. Several factors may explain the coagulopathy observed and thus the dramatic bleeding in a surgical patient with impaired haemostasis (35.5°C), bleeding was still active and justified a second surgical look 5 h later. Active bleeding from a diaphragmatic vein, a pulmonary wound and the lower aortic graft anastomosis were surgically corrected. Perioperative blood loss required massive transfusion (13 units of blood, 12 units of fresh frozen plasma and 10 units of platelets).

Further in the ICU was marked by the occurrence of a collection near the aortobifemoral graft within a month, associated with sepsis due to Enterococcus gallinarum. Despite targeted antibiotics (vancomycin and gentamycin), the patient remained septic.

Surgical excision of the abscess together with an allograft replacement of the thoracic prosthesis was performed at day 34 under hypothermic cardiopulmonary bypass. Preoperative haemostasis was normal. Aprotinin was administrated to prevent fibrinolysis. Thoracic aortic cross-clamping lasted 23 min at 25°C. Diffuse non-surgical bleeding developed after weaning off cardiopulmonary bypass, despite heparin reversal by protamine. It required the administration of 13 units of blood, 5 of fresh frozen plasma and 10 of platelets before the incision could be closed.

During the immediate postoperative period, the patient remained unstable with active bleeding through the drains requiring further transfusion (5 units of blood, 4 of fresh frozen plasma, 10 of platelets and 3 g of fibrinogen), administration of aprotinin and continuous haemodynamic support with norepinephrine (up to 12 mg h$^{-1}$). Despite normal in vitro haemostasis tests and normothermia, bleeding through the drains was >500 mL h$^{-1}$ justifying the administration of a 90 µg kg$^{-1}$ of rFVIIa. This was followed by the termination of bleeding. Thereafter, norepinephrine requirements markedly decreased (3 mg h$^{-1}$), and no further transfusion was required after 2 h. Clinical and biological follow up did not highlight any side-effect. The patient’s condition gradually improved and he was later discharged for rehabilitation.

Analysis of these events shows that rFVIIa was effective in controlling massive postoperative bleeding in a surgical patient with impaired haemostasis due to both sepsis and to uninterrupted preoperative antiplatelet therapies. Several factors may explain the coagulopathy observed and thus the dramatic blood loss and massive transfusion required in this patient. First, active perioperative bleeding and coagulation activation due to tissue factor release at the site of vascular injury is markedly increased in cases of repeat surgery and/or sepsis [3]. Second, despite normal preoperative haemostasis tests, aspirin and clopidogrel induced important platelet dysfunction, while these drugs could not be withdrawn due to the emergency conditions. Both aspirin and clopidogrel therapies were routinely prescribed to the patient by his general practitioner because of coronary disease. Third, supra-coeliac aortic cross-clamping is associated with increased bleeding due to increased fibrinolysis secondary to splanchnic ischaemia, and due to heparin administration [4].

Our patient experienced massive postoperative diffuse bleeding inaccessible for surgical haemostasis, despite warming, transfusions (according to blood loss, in vitro haemostasis results and French
recommendations), antifibrinolytic (aprotinin) therapy and appropriate calcium replacement. Particular attention must be paid to routine preoperative antiplatelet therapy. First, they justified platelet transfusion (12 units) prior to the first surgery. Second, serum clearance of these therapies was dramatically increased due to massive bleeding.

The administration of rFVIIa was associated twice with rapid termination of postoperative bleeding. At these therapeutic doses, plasma level of rFVIIa is about 100 times higher than endogenous FVIIa level [5]. rFVIIa binds with tissue factor at the site of injury and with activated platelets, leading ultimately to a burst in thrombin formation [1]. This case confirms the previous reports of the efficacy of rFVIIa as a rescue therapy in several situations of severe postoperative bleeding. No thromboembolic complication was observed in this patient. However, we think that these events illustrate some important recommendations that have been recently emphasized concerning the use of rFVIIa in these off-label conditions [6]. First, rFVIIa is only an adjunctive haemostatic therapy that should not replace surgery and or embolization when they are required. In our patient, surgical bleeding required a second look and it is not likely that rFVIIa could have solved this problem. Second, rFVIIa should not replace the correction of the various factors that are known to interfere with haemostasis: platelet, coagulation factors, fibrinogen, red cells, calcium and temperature [1,6]. Nevertheless one can wonder whether an earlier administration of rFVIIa should have been able to decrease the amount of transfusion required in this patient. rFVIIa is a costly drug but the cost of transfusion was greater in our patient.

We administered a first dose of 90 µg kg⁻¹ of rFVIIa which is the recommended dose in France for off-label use in severe bleeding. In other reports of perioperative bleeding or trauma, doses between 60 and 144 µg kg⁻¹ have been used [2,7]. However, in severe trauma patients, a higher dose has been recently examined in a randomized study. In our patient, the dose used appeared to be sufficient since bleeding stopped but it should be emphasized that the rate of bleeding was not very high. In patients with higher rate of bleeding, one can suspect that the clearance of rFVIIa is artificially increased by blood loss, thus requiring administration of higher doses. This important point warrant further studies.

In conclusion, our patient experienced massive bleedings after repeat septic vascular abdominal aortic surgeries. The bleeding was twice successfully controlled using i.v. rFVIIa. Anaesthesiologists should be aware that rFVIIa may represent an efficient therapy if conventional therapy failed to control bleeding in such clinical situations.

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References
Subanaesthetic doses of ketamine impair cardiac parasympathetic regulation

EDITOR:

Ketamine is a phencyclidine anaesthetic agent with a stimulatory effect on the cardiovascular system and an analgesic action. In addition to N-methyl-D-aspartate (NMDA) receptor antagonism, ketamine has interactions also with opioid, monoaminergic, non-NMDA glutamate and both nicotinic and muscarinic cholinergic receptors [1]. The use of ketamine is often limited by its adverse effects: vivid dreaming, unpleasant hallucinations, nausea and vomiting. However, during the past few years, the use of low-dose ketamine has gained increasing interest in anaesthesiology. Low-dose ketamine has been considered a safe adjuvant analgesic to opioids, local anaesthetics or other analgesic agents [2]. Low doses of ketamine have also been given in combination with, for example, midazolam, to provide intraoperative sedation and amnesia and during propofol anaesthesia to attenuate propofol-induced hypoventilation and to provide earlier recovery of cognition [3].

In general, anaesthetic agents inhibit cholinergic efferent vagal activity in the heart, which, in turn, is manifested as reduced high-frequency (HF) heart rate variability [4]. Such an effect has also been observed after anaesthetic doses (2 mg kg⁻¹) of ketamine [5]. Particularly in patients with diseases impairing the cardiac autonomic regulation (e.g. heart diseases, diabetes mellitus, autonomic neuropathy), highly parasympatholytic agents put an additional strain on the control of cardiac function. Therefore, we wanted to investigate the impact of subanaesthetic doses of ketamine on cardiac parasympathetic regulation.

After Ethics Committee approval and written informed consent, a total of 16 male volunteers (18–27 yr, 165–188 cm, 60–91 kg) were enrolled in this open, nonrandomized trial. Nine subjects were participants in a positron emission tomography imaging study that evaluated the effect of subanaesthetic ketamine on regional cerebral blood flow and oxygen consumption [6]. An additional seven subjects served as controls. The health of the volunteers was determined with clinical examinations including a 12-lead electrocardiogram (ECG). They refrained from using alcohol or any medication for 48 h and fasted overnight before the study.

The subjects were equipped with a portable digital Holter ECG recording device (Oxford Medilog FD-3; Oxford Medical Ltd., Woking, UK). During the ECG recordings, the subjects lay in a supine position and breathed spontaneously at approximately 12–13 breaths min⁻¹ [6]. After baseline measurements, racemic ketamine was administered as an intravenous (i.v.) infusion targeting at three pseudo-steady state serum concentrations of 30, 100 and 300 ng mL⁻¹, at 50 min intervals. The actual measured serum concentrations were 37 ± 8, 132 ± 19 and 411 ± 71 ng mL⁻¹ (mean ± SD), respectively [6]. 1000-beat segments of ECG data at baseline and at the end of each concentration level were subjected to analysis of heart rate variability. Equal measurements were performed in the control group, but without medication.

From the Holter ECG recording, stationary time series of consecutive R–R intervals were generated and subjected to power spectral analysis with fast Fourier transformation (WinCPRS software package; Absolute Aliens Oy, Turku, Finland). After linear detrending of the signals, total power of R–R interval variability was generated and the HF power was then extracted from the total power by integration over the frequency band 0.15–0.40 Hz [4]. The HF power is considered to reflect the parasympathetic activity in the heart.

The differences in treatment (ketamine, control) effects on the mean R–R interval and HF power were evaluated with repeated measurements analysis of variance (RM ANOVA, SAS version 8.02; SAS Institute Inc., Cary, NC). In order to eliminate the impact of possible differences in baseline levels, RM ANOVA was performed on changes from baseline. To achieve normal data distribution the HF power was log-transformed prior to statistical analysis. The statistical model included fixed effects for treatment, concentration and treatment-by-concentration interaction. When a significant treatment or treatment-by-concentration interaction effect was detected, analyses were continued with pairwise comparisons using t-tests within the same model. Both unadjusted and Bonferroni’s test adjusted P-values are presented. Two-sided P-values of <0.05 were considered statistically significant.

The main results are presented in Table 1. At baseline, the mean ± SD HR was 58 ± 9 beats min⁻¹. At 30 ng mL⁻¹, ketamine had no significant influence on HR or HF power. At 100 ng mL⁻¹, the average HF power was decreased by 41% from baseline (ketamine vs. control, P = 0.013). At 300 ng mL⁻¹,
the HR increased to $67 \pm 10$ beats min$^{-1}$ and the average HF power was decreased by $57\%$ from baseline (ketamine vs. control, $P = 0.050$). The difference between groups in the baseline HF variability values was mostly due to one participant in the ketamine group, whose HF power was $6899$ ms$^2$.

Our main finding is that even small, subanaesthetic doses of ketamine can reduce markedly the HF component of heart rate variability, implying a distinct parasympatholytic influence [4]. It should be noted, however, that this effect is quite moderate in comparison with total parasympathetic blockade [4].

There are several possible mechanisms by which ketamine can suppress cholinergic efferent vagal activity. Ketamine is known to exert a direct inhibitory effect on both nicotinic and muscarinic acetylcholine receptors [1] and it can also inhibit NMDA receptor-mediated acetylcholine release, and nicotinic excitation in cardiac parasympathetic neurons in the brainstem.

Ketamine also has a well-known sympathomimetic action, which presumably arises from direct stimulation of central nervous system structures. In plasma concentrations of approximately $200–300$ ng mL$^{-1}$, ketamine increases markedly the adrenaline and noradrenaline plasma levels. The sympathetic excitation is evidently the reason for the ketamine-induced hypertensive effect during 100 and $300$ ng mL$^{-1}$ concentrations [6]. Normally the blood pressure rise would trigger the arterial baroreceptor reflex, leading to increased parasympathetic activity in the heart. Our opposite findings of decreased vagal activity and increased HR (at $300$ ng mL$^{-1}$) seem to indicate impaired baroreflex regulation and lend support to a direct parasympatholytic effect of ketamine. This attenuation of baroreceptor reflex possibly originates from the interaction of ketamine with the NMDA receptor in the nucleus tractus solitarius [7].

Furthermore, the sympathetic activation may also partly explain the observed cardiac anticholinergic influence, since adrenaline and noradrenaline can inhibit acetylcholine release in the atria, and noradrenaline the function of the dorsal motor nucleus of the vagus nerve.

In conclusion, even subanaesthetic doses of ketamine can exert a measurable anticholinergic effect in the heart, which is, however, quite moderate in comparison with total parasympathetic blockade.

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Table 1. Mean R–R interval and high-frequency (HF) power of R–R interval variability in the ketamine group ($n = 9$) and control group ($n = 7$).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>Baseline</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_s$ (ng mL$^{-1}$)</td>
<td>Ketamine</td>
<td>0</td>
<td>30</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Mean R–R interval (ms)</td>
<td>Ketamine</td>
<td>1056 ± 144</td>
<td>1043 ± 165</td>
<td>1016 ± 129</td>
<td>907 ± 126</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1032 ± 76</td>
<td>ns</td>
<td>1024 ± 89</td>
<td>1033 ± 98</td>
</tr>
<tr>
<td>HF power (ms$^2$)</td>
<td>Ketamine</td>
<td>2529 ± 1975</td>
<td>2395 ± 2532</td>
<td>1487 ± 1197</td>
<td>1081 ± 828</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1525 ± 1065</td>
<td>1741 ± 788</td>
<td>1303 ± 608</td>
<td>1390 ± 608</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD. Repeated measurements analysis of variance was performed on changes from baseline.

$^a$Significant treatment-by-concentration interaction effect ($P < 0.001$).

$^b$Significant treatment effect ($P = 0.014$).

$^c$Bonferroni's test adjusted $P$-values.

$C_s$: targeted ketamine concentration in serum; ns: non-significant.
Intraoperative metamizol as cause for acute anaphylactic collapse

EDITOR:
The pyrazolone derivative metamizol is used clinically for its analgesic, antipyretic, anti-inflammatory or spasmylytic properties [1,2]. Metamizol is commonly used throughout Europe and South America. In contrast, metamizol is not used in other countries (e.g. the USA) due to the ongoing controversy regarding its potential to precipitate allergic agranulocytosis [3]. Only little is known about the potential of metamizol to precipitate acute anaphylactic reactions. In fact, a study on the risk of anaphylactic reactions associated with the in-hospital application of frequently used medications demonstrated only a relatively low risk of acute anaphylactic reactions associated with metamizol, similar to paracetamol [4]. However, some very recent reports on the use of metamizol during the perioperative period describe severe allergic reactions associated with its intravenous (i.v.) application [5–7]. Similarly, we here report two patients in whom intraoperative use of i.v. metamizol was immediately followed by cardiocirculatory collapse. Such reports suggest that the risk of metamizol associated severe anaphylactic reactions may be underestimated.

Case report

Case 1. A 58-yr-old male patient presented to the hospital for revision of an intracranial neurostimulator that had been implanted previously in the treatment of Parkinson’s disease. His past medical history was only remarkable for Parkinson’s disease. He had no known drug allergies accept a skin reaction associated with the use of oral tilidin. Prior to the operation, the patient was premedicated with midazolam and anaesthesia was induced with sufentanil 15 µg and propofol 175 mg. Tracheal intubation could be performed easily after muscle paralysis was obtained with rocuronium 175 mg. At the end of the operation, 2500 mg of metamizol were given i.v. as a short infusion to prevent postoperative pain. Immediately after completion of the infusion, the patient became hypotensive (blood pressure (BP) 50/30 mmHg), bronchospastic and developed generalized erythema. As the patient became pulseless, chest compressions were initiated and i.v. epinephrine, 1 mg every 2 min was given. After 15 min of cardiopulmonary resuscitation (CPR), an episode of ventricular fibrillation could be converted to sinus rhythm with electrical defibrillation. At this point, the patient had a palpable pulse and a BP of 90/60 mmHg. Epinephrine was continued as an infusion and the patient was transported to the intensive care unit (ICU) in a stable condition. Further investigations ruled out myocardial infarction and pulmonary embolism. Shortly after, he was extubated and subsequently transferred to a ward and discharged home in good condition. An allergic study showed dramatically elevated tryptase plasma levels (32.4 µg L⁻¹ at 6 h after exposure) and skin prick testing showed a strong reaction to metamizol (0.5 cm skin wheal) at a dilution of 1 : 1000. All other substances tested (normal saline, all anaesthetic and antibiotic medications used during the perioperative period) did not provoke a skin reaction.

Case 2. A 52-yr-old male presented to the hospital with a herniated disk and was scheduled to undergo

References


lumbar discectomy. His past medical history was significant for transient ischaemic attacks and vascular encephalopathy. The patient was not aware of any previous allergic reactions. For the operation, the patient was premedicated with midazolam, 1 mg i.v. and anaesthesia was induced with sufentanil 15 μg and propofol 200 mg. After muscle paralysis was obtained with rocuronium 30 mg, tracheal intubation could be performed easily and anaesthesia was maintained throughout the operation with isoflurane. The patient was placed in a prone position and received i.v. cefuroxime 3 g as perioperative antibiotic prophylaxis. At the end of the surgery, metamizol 2500 mg was given as an i.v. infusion to decrease postoperative pain. Within minutes, the patient became hypotensive (BP 51/31 mmHg), developed bronchospasm and generalized erythema. He was immediately turned on his back and resuscitated with epinephrine 1.5 mg and rapid i.v. volume infusion (2500 mL of hydroxyethyl starch 130/0.4). In addition, the patient received prednisolone 1000 mg, dimetindene maleat 8 mg and cimetidine 400 mg. Subsequently, the bronchospasm and hypotension resolved and the patient was transported to the ICU. An investigation for pulmonary embolism or myocardial infarction was negative. The patient could be extubated after 6 h and was subsequently transferred to a ward. Neurological investigations were unremarkable. Again, the allergic study showed a severe skin reaction to metamizol while all other substances (normal saline and all anaesthetic and antibiotic medications used perioperatively) tested negative.

Discussion

Metamizol is frequently used in several European and South American countries as an antipyretic and analgesic medication [4]. In contrast, the Food and Drug Administration in the USA has not approved metamizol due to its potential to elicit an antibody related bone marrow depression causing agranulocytosis [3,8]. In addition, cutaneous allergy to metamizol has been reported previously [9]. However, very recent reports on the perioperative use of i.v. metamizol also suggest, that acute allergic reactions leading to cardiovascular collapse may be related to this medication [2,5,7]. Similarly, we report here two patients who received surgery in our hospital within a time period of only 6 months in both of whom we observed an acute anaphylactic collapse immediately after a metamizol infusion. These recent reports suggest, that the potential of metamizol not only to cause a chronic form of allergy (agranulocytosis) but also to cause acute allergic reactions may have been underestimated. If such reports continue, perioperative physicians should consider alternate means of controlling pain or fever other than i.v. metamizol.

The development of an acute allergic reaction results from a release of preformed granulocyte-associated mediators, membrane-derived lipids, cytokines and chemokines, when an allergen interacts with immunoglobulin E (IgE) antibodies bound to mast cells or basophils [10]. Therefore, patients with an IgE-mediated acute allergic reaction have usually had previous exposure to the allergen or a structurally related antigen, thus inducing the formation of IgE antibodies. Similarly, both patients reported previous exposure to metamizol within the last 6 months. However, there are no data available to conclude after which time following a previous exposure, the risk of allergic reactions is decreased. Therefore, it appears critical to follow further publication of acute adverse reactions to i.v. metamizol. If such reports continue, the safety of i.v. metamizol needs to be reconsidered. In the meantime, careful observation as well as readiness for treatment of acute allergic reactions seem justified if i.v. metamizol is given in the perioperative period.

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References

