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Correspondence

Perioperative management of a patient with severe factor XII deficiency

EDITOR:

Factor XII deficiency is a hereditary state that is usually discovered because of an unexpected prolongation of activated partial thrombin time (aPTT) during preoperative evaluation. We report the perioperative management of an orthopaedic patient with severe factor XII deficiency.

An 18-yr-old male (height: 175 cm, weight: 72 kg) with a lateral malleolar fracture was transferred to our institution from a county hospital for operative stabilization. A pre-anaesthetic laboratory screen during his first admission revealed an extremely prolonged aPTT that did not return to normal after the transfusion of 3 units of fresh frozen plasma (see Table 1). He had no relevant past medical history and he did not report any symptoms of abnormal haemostasis after traumatic injuries. The physical examination showed no pathologic findings, except for painful ankle oedema. A detailed investigation of haemostasis was performed, including the assessment of protein C, protein S, antithrombin, lupus anticoagulant, prekallikrein and activated protein C resistance. The only pathologic finding was a significant reduction in factor XII activity (4.6%, normal range >80%). This explained the marked prolongation in aPTT. The patient's haemostasis was regarded as sufficiently effective [1]. Nevertheless, he was considered at increased risk for thromboembolic complications and prophylaxis was started with reviparin sodium, 3500 anti-Xa units subcutaneously once daily [2]. The following morning (12 h after reviparin administration), an epidural catheter was placed atraumatically in L4–L5 interspace and the patient underwent an uneventful operative stabilization under epidural anaesthesia with levobupivacaine 0.5% 15 mL plus morphine 3 mg. No abnormal bleeding was observed during the 40 min of the surgical procedure. Postoperative analgesia consisted of patient controlled epidural analgesia with morphine (2.5 mg morphine bolus, 30 min lockout) and parecoxib sodium 40 mg once daily intravenously or intramuscularly. Pain relief was successful, allowing early mobilization. The epidural catheter was removed on the third postoperative day. The postoperative period was uneventful with no signs of deep venous thrombosis or spinal cord compression. Prophylaxis with low-molecular-weight heparin was continued until the 5th postoperative day and the patient was discharged.

Table 1. PT and aPTT.

	PT (s) (normal range 10.1–12.9)	aPTT (s) (normal range 24–35)
Preoperative screen	12.2	238
Immediately after 3 units of fresh frozen plasma	12.3	46
20 h after fresh frozen plasma	12.2	48

PT: prothrombin time.

The factor XII protein is synthesized in the liver. It has a half-life of about 60 h and its concentration in normal plasma is 30 $\mu g\,mL^{-1}$. Factor XII deficiency is inherited in an autosomal recessive pattern. Factor XII, prekallikrein and high-molecular-weight kininogen are the major factors involved in the so-called 'contact' phase of coagulation. Factor XII is activated by plasma kallikrein during endothelial injury. Activated factor XII is the first component of the intrinsic pathway of the coagulation cascade, while simultaneously, factor XII fragments activate plasminogen during the initiation of normal fibrinolysis. The overall prevalence of factor XII deficiency in the normal population is estimated as 1.5–3.0%, with the severe factor XII deficiency (activity <1%) in a minority. In these rare individuals, aPTT is seriously prolonged with values exceeding 120 s [3]. We believed that our patient had severe factor XII deficiency because of the extreme prolongation of the initial aPTT (238 s) and the significantly decreased

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factor XII activity (4.6%) 24 h after the transfusion of three units of fresh frozen plasma.

The question arises as to why our patient did not report a bleeding tendency in spite of the very low factor XII levels. Although factor XII is necessary for *in vitro* coagulation during aPTT testing, its presence seems unimportant for *in vivo* haemostasis. The role of factor XII and other contact factors in coagulation is not so clear and the extrinsic pathway is sufficient for the initiation of coagulation in human beings [1]. Patients with even severe factor XII deficiency are free of haemostatic problems. Therefore, transfusion with fresh frozen plasma or cryoprecipitate for the correction of low factor XII plasma concentration in patients with isolated severe factor XII deficiency is not justified.

Patients with severe factor XII deficiency do not have a bleeding tendency. On the contrary, they have a high rate (8–10%) of premature venous thromboembolic events [1]. Factor XII deficiency may lead to hypercoagulability through a defective activation of fibrinolysis. Surgical trauma and immobilization increase the risk of thromboembolic complications. Severe factor XII deficiency places the patient at a moderately increased thromboembolic risk level even during minor surgery and necessitates the application of effective preventing measures such as low-molecular-weight heparin administration, early mobilization and regional anaesthesia [2,4]. Epidural anaesthesia and analgesia have favourable effects on fibrinolysis and offer conditions for sufficient postoperative analgesia and early mobilization [5]. If the placement and removal of an epidural catheter are carefully timed with the low-molecular-weight heparin administration, epidural anaesthesia can be used safely in the perioperative anaesthetic management of these patients.

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Anaesthetic management in vitreo-retinal surgery

EDITOR:
We read about the analgesic effects of sub-Tenon's block in vitreo-retinal surgery under general anaesthesia by Farmery and colleagues with great interest [1]. Their study reported that all the patients scheduled for vitreo-retinal surgery under general anaesthesia received a standardized general anaesthetic technique consisting of propofol infusion and 50% oxygen in nitrous oxide. The duration of administration of nitrous oxide was not mentioned. Among the 43 patients, 16 had already been treated by injection of gas/oil. The movement of nitrous oxide into gas-containing spaces in the body has been known for a long time. The use of nitrous oxide during vitreous surgical procedures in which gas bubble injection is used will lead the bubble to increase in size and elevate the intraocular pressure. Stinson and Donlon, in 1982, conducted a study to predict the effect of 70% nitrous oxide anaesthesia on the volume of the intravitreal bubble by using a mathematical method.

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They suggested that nitrous oxide, independent of the duration it is used, causes an increase in volume of the injected gas bubbles in varying sizes, with the risk of occlusion of the central retinal artery [2]. In addition, after vitreous surgery in which a gas bubble was used for retinal re-attachment, subsequent administration of nitrous oxide should be avoided until the bubble is absorbed. Re-administration of nitrous oxide may cause occlusion of the central retinal artery by moving into the pre-existing intravitreal bubbles, leading to blindness [3,4].

To avoid these complications, we have been using remifentanil infusion ($0.05\,\mu g\,kg^{-1}\,min^{-1}$) for its analgesic effect instead of nitrous oxide due to the fact that nitrous oxide is 35 times more soluble in blood than nitrogen (the major component of air). We use 50% oxygen in air with volatile anaesthetics [5]. We have administered a remifentanil infusion to 50 patients undergoing vitreous surgery. At the end of surgery, 15 min before anaesthesia was stopped, a single dose of metoclopramide and metamizol were administered intravenously. During surgery, we did not observe any large swings in arterial pressure or increase in postoperative opioid requirement leading to nausea and vomiting, as reported by Farmery and colleagues. We have been able to provide smooth intraoperative haemodynamic conditions by using a remifentanil infusion with volatile anaesthetic agents.

We recommend our technique of anaesthesia including remifentanil infusion instead of nitrous oxide in vitreo-retinal surgery in order to avoid the undesirable effects of nitrous oxide on intraocular pressure. It is important to know of the existence of a residual intravitreal gas bubble injected in recent vitreal surgery, so that nitrous oxide can be avoided.

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Anaesthetic management of the Prader–Willi syndrome

EDITOR:
Prader–Willi syndrome (PWS) is a rare inherited multisystem disorder first described by Prader, Labhart and Willi in 1956. Major features include muscular hypotonia, skeletal abnormalities, mental alterations and obesity. Many cases have been subsequently described in the literature and associations with cardiopulmonary disorders, endocrine disorders and sleep apnoea syndrome have been reported. These associated conditions may lead to difficulties in anaesthetic management. We describe the anaesthetic management of four patients with PWS scheduled for elective surgery and review implications of perioperative management [1].

Case 1: A 4-yr-old male patient weighing 25 kg was scheduled for elective laparoscopic left testicular retrieval and contralateral orchidopexy. Preoperative assessment revealed adiposity, airway obstruction and sleep apnoea syndrome. Chest X-ray had suggested a cardiac abnormality which was not confirmed by transthoracic ultrasound although mild mitral stenosis was discovered. Concomitant diseases included several previous episodes of febrile seizures and right bundle branch block. Preoperative blood glucose levels were within the normal range. Anaesthesia was induced with fentanyl and propofol, tracheal

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intubation was facilitated with rocuronium and anaesthesia maintained with fentanyl, propofol and nitrous oxide in oxygen. Anaesthesia was uneventful and at the end of surgery nalbuphine hydrochloride was given to reverse the effect of the fentanyl and to initiate spontaneous breathing.

Case 2: A 4-yr-old male patient weighing 27.5 kg was scheduled for elective Luque de-rotation and fixation of scoliosis as a consequence of spinal muscular atrophy Type III. Preoperative evaluation revealed adiposity and a history of pneumonia but no evidence of reactive airway disease. Anaesthesia was induced with midazolam, fentanyl and thiopental, and tracheal intubation facilitated with rocuronium. Anaesthesia was maintained with sevoflurane and remifentanil, and was uneventful. Intraoperative blood glucose levels were within the normal range.

Case 3: A 4-yr-old male patient weighing 32 kg was scheduled for elective tonsillectomy. Preoperative evaluation revealed sleep apnoea syndrome and history of pneumonia. Anaesthesia was induced with midazolam and thiopental and tracheal intubation was facilitated with rocuronium. Sevoflurane and fentanyl were used for maintenance. At the end of anaesthesia the onset of spontaneous breathing was delayed. This was not considered to be attributable to fentanyl and theophylline was administered intravenously to initiate spontaneous breathing.

Case 4: A 22-yr-old male patient weighing 128 kg was scheduled for elective dental surgery. Preoperative evaluation revealed severe mental retardation, morbid obesity, a very short neck, sleep apnoea syndrome, a history of pneumonia, and both restrictive and obstructive lung disease. Insulin-dependent diabetes mellitus (Type II) had been previously diagnosed. Before surgery, the patient was highly aggressive and anaesthesia had to be induced using intramuscular ketamine. Subsequent to venous cannulation, midazolam was given and tracheal intubation performed using a fibreoptic technique. Sevoflurane, rocuronium and fentanyl were used for maintenance of anaesthesia. Blood glucose levels were closely monitored, and supported using a glucose and insulin infusion. During anaesthesia oxygenation was difficult and high inspiratory pressures were necessary. Wheezing was audible on auscultation, and theophylline and prednisolone were administered resulting in partial resolve of airway spasm. Postoperative recovery was uneventful.

Clinically, PWS is characterized by a biphasic profile. Early in childhood, muscular hypotonia, hypogonadism and feeding abnormalities combined with growth retardation are the most prominent symptoms. In later childhood and adolescence hyperphagia, obesity and psychological disturbances, mental retardation and obsessional behavioural problems become predominant features [1]. Physical symptoms include short stature in approximately 90% of cases caused by muscular hypotonia, subsequent hypokinesia and feeding difficulties. Furthermore, dysmorphic features such as small hands and feet become pronounced with increasing age [1].

Mental problems develop from age 5 and include temper tantrums, stubbornness and verbal perseveration. It has been suggested that only some 5% of PWS patients have a normal IQ. Some of these characteristic defects as well as possibly associated diseases warrant close scrutiny in the perioperative management of the patient.

Perhaps the most important factor in the preoperative assessment and premedication of the PWS patient is muscle weakness. In general, this hypotonia may facilitate gastric aspiration at any time [2]. The decreased motility of the gastrointestinal tract especially heightens the risk of perioperative aspiration [3], and the sequelae of aspiration may be more severe due to limited pulmonary reserves [3]. Three patients in our case report series featured a history of pneumonia, underlining the importance of muscular hypotonia in these patients. The perioperative aspiration risk is further exacerbated by a high incidence of rumination and lowered oesophageal sphincter tone [3]. Cases of food regurgitation after more than 10 h of strict fasting have been reported. This may not only be due to increased and continuous rumination, but also due to the highly developed food seeking and stealing behaviour associated with hyperphagia. Therefore, Sloan and Kaye suggested that only closely supervised PWS patients should be considered to have an empty stomach when nil by mouth [3].

Diabetes mellitus is a frequent facet of PWS developing in later childhood, although there is uncertainty as to whether this constitutes a symptom of PWS or whether it is a consequence of morbid obesity [4]. In one series of PWS patients the incidence of Type II diabetes mellitus was 19% of which more than 50% were insulin dependent [4]. This is of substantial interest to the anaesthetist, since normoglycaemia should be one key concern. It has been reported that PWS patients continue to utilize circulating glucose to manufacture fat rather than to satisfy basal energy needs [2].

Cassidy and colleagues described an incidence of restrictive pulmonary disease of 80–90% in PWS patients aged over 30. Major factors include morbid obesity, thoracic muscle weakness and an increased incidence of kyphoscoliosis [1]. The incidence of hypertension in older PWS patients ranges from 17% to 32% and may be correlated with obesity [1]. PWS patients may have abnormally thick and viscous saliva and so the routine prescription of atropine as premedication may not be appropriate [5].

Great care should be directed towards perioperative fluid and electrolyte balance, hepatic function and nutrition, especially in patients following intestinal bypass procedures [3]. The tendency of PWS patients to utilize circulating glucose to manufacture fat should prompt blood glucose monitoring at regular intervals. Thermoregulatory responses seem to be blunted in patients with PWS probably due to abnormal parasympathetic regulation of central thermal control combined with abnormal peripheral vasomotor responses [6]. It has been suggested that regional techniques and non-steroidal anti-inflammatory drugs may be more beneficial than opioids in the immediate postoperative period [2].

Patients with PWS are at increased risk of postoperative hypoxia. This has been linked to deranged awake responses to alterations in blood oxygen and carbon dioxide (CO_2) content. Delayed responses to these stimuli have been described in PWS independent of the degree of obesity [7]. It has been suggested that the threshold of CO_2 response is elevated independent of obesity with the slope of the ventilatory response to CO_2 being worse in obese than non-obese patients. Recently, a decreased sensitivity of peripheral chemoreceptors to changes in blood oxygen and CO_2 has been demonstrated. Current literature suggests a primary abnormality in the peripheral chemoreceptor pathways or hypothalamic alterations as the most plausible mechanisms [7]. Furthermore, the arousal threshold from sleep under hypercapnia and hypoxia is abnormal in PWS patients which may be of significance in the immediate postoperative period.

In conclusion, we suggest that during the perioperative period in PWS patients, blood glucose should be carefully monitored, and the increased risk of aspiration and postoperative apnoea should be considered.

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Is the Datex-Ohmeda® M-NMT module a research quality instrument?

EDITOR:
I would like to congratulate Drs Motamed and colleagues on their study comparing the Datex-Ohmeda M-NMT® neuromuscular transmission module with conventional mechanomyography [1]. Their results are much more encouraging than those previously reported by Dahaba and colleagues [2]. The latter authors found during recovery from neuromuscular block, a bias (Bland–Altman analysis) of −3% between the train-of-four ratio measured by the two

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monitors, and limits of agreement of −28% to +0.22%. Motamed and colleagues in contrast report measured NMT (M-NMT) to mechanomyography train-of-four ratio bias of only 1.3% with 95% limits of agreement of −13% to +14%. They conclude that the "M-NMT is adequate for clinical practice, but for (neuromuscular) research … the greater accuracy of a force transducer is still necessary." I would suggest, however, that their analysis of the research potential of the M-NMT is potentially too harsh.

In an earlier study from their department [3] these authors showed that the onset time of vecuronium was the same in both arms when measured simultaneously with mechanomyography. They therefore seem to have concluded that mechanomyographic measurements from contralateral limbs should vary little if at all. Clearly, this is not necessarily the case. Kirkegaard-Nielsen and colleagues [4] very carefully did the study of simultaneously recording mechanomyographic responses in contralateral arms and found that the average train-of-four values were little different but the 95% limits of agreement for individual readings ranged from +11% to −7% percentage points. They concluded that "The substantial variation between simultaneous mechanomyographic recordings of neuromuscular transmission obtained in contralateral arms suggests that this factor should be taken into account when studying new neuromuscular monitoring techniques using the two-arm technique." The confidence limits observed by Motamed and colleagues for simultaneously measured NMT and mechanomyographic responses are not greatly different from those reported by Kirkegaard-Nielsen.

It is premature to suggest that the M-NMT module can or should be adopted as a reliable research instrument. However, it is also too early to conclude that this monitor has no promise as a research tool.

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A Reply

EDITOR:
We are grateful to Dr Kopman for carefully reading our article and for his encouraging comments about the M-NMT monitor. As we explained in our article, we did not assess the onset of neuromuscular block due to the rapidity of onset of rocuronium. In addition, the monitor does not calculate the twitch height. Comparisons can only be made during recovery of train-of-four ratios. Thus, the results of our single bolus study based only on comparisons of train-of-four ratios did not permit us to propose that the M-NMT monitor could be used as a reliable and accurate research monitor. We agree with Dr Kopman that further studies are necessary before using this device for the purposes of neuromuscular research.

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