

## Acquired Factor VIII Inhibitor

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PERSISTENT or uncontrolled bleeding is one of the most feared consequences of any surgical procedure. Numerous factors can contribute to its etiology. Among these, both inherited and acquired disorders of coagulation and/or thrombocyte function need to be taken into account.<sup>1,2</sup> Acquired hemophilia can be caused by antibodies to coagulation factors. Antibodies can arise in hemophilic or non-hemophilic patients. In the former case, patients are treated with Factor VIII concentrate and develop alloantibodies. Nonhemophilic patients produce autoantibodies (mostly against Factors VIII and IX), and this is believed to be an autoimmune reaction.<sup>3</sup> The estimated annual incidence rate of clinically apparent bleeding caused by autoantibodies is 1.48/million inhabitants,<sup>3</sup> or approximately 450 patients in the United States per year. The incidence of the disease seems to be increasing; it is more prevalent in elderly patients and it can be successfully treated if diagnosed adequately and early.<sup>3</sup> Here, we present a case of massive and long-lasting bleeding in a nonhemophilic patient undergoing extensive visceral surgery.

## Case Report

A 57-yr-old woman (158 cm, 74 kg) presented with a long-lasting history of upper abdominal pain and a diagnosis of chronic pancreatitis. On computed tomographic and nuclear magnetic resonance imaging the pancreatic duct was dilated and obstructed by a calcific structure. Endoscopic extraction of a stone had failed by endoscopic retrograde cholangiopancreatography. Coagulation studies were normal, with a mildly prolonged activated partial thromboplastin time (aPTT; 44 s, normal value 20–40 s).

Three months later, the patient decided to undergo surgery because of persistent pain. She was in good general health, employed full-time, and

physically active. Her past medical history revealed mild hypertension, minor obstructive sleep apnea, and dyspnea on exertion without angina. She had a smoking history of 20 packyears. Her hypertension was treated with metoprolol and lisinopril. She had undergone several minor abdominal surgeries without complications. The interview and physical examination were otherwise unremarkable. She denied any signs of past or present abnormal bleeding or a family history thereof. Laboratory values were within normal range, with the exception of an aPTT of 78 s, which was not verified preoperatively. The patient underwent a laterolateral pancreaticojejunostomy as a drainage procedure, which was uneventful.

Postoperatively, a persistently elevated aPTT as well as a progressively more severe anemia (nadir, hemoglobin 4.9 mg/dl on postoperative Day [POD] 2) were noticed. Erythrocyte concentrates and fresh frozen plasma were transfused. Moderate bleeding persisted (two units of blood/day). Surgical reexploration demonstrated diffuse bleeding activity. On POD 4, an extensive coagulation workup demonstrated a severe Factor VIII deficiency (4%) as the most significant pathologic value (table 1). On direct questioning the patient recalled that she had developed an extensive hematoma on her lower leg after a minor trauma several weeks before surgery. The patient received Factor VIII with von Willebrand factor (12,000 units over 3 days; Hemate, CSL Behring, Marburg, Germany) and bleeding further increased. On POD 8, the diagnosis of an acquired Factor VIII deficiency was established when a Factor VIII inhibitor of 117 Bethesda units (fig. 1) was demonstrated. The patient was transferred to our intensive care unit. Once the diagnosis was established the patient was treated with activated prothrombin complex concentrate (aPCC; FEIBA [Factor VIII bypassing activity], Vienna, Austria) at a dose of 100 units/kg twice daily. Bleeding continued and treatment was switched to rFVIIa (up to 90 units/kg every 2 h; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark; fig. 1A). Simultaneously, inhibitor elimination was started using corticosteroids (prednisolone 70 mg/day), plasmapheresis with adsorption of immunoglobulins (Therasorb-Ig; Miltenyi Biotec, Bergisch Gladbach, Germany) three days per week, followed by intravenous immunoglobulins (30 mg/day for 4 days; Biotest, Dreieich, Germany). The patient received a total of 50 units of packed red blood cell concentrations (fig. 1A), and bleeding was controlled at POD 14. Catastrophic bleeding started again on POD 29. Angiographic studies demonstrated a leak from the gastroduodenal artery that could not be controlled by endovascular coiling; it required surgical ligation and repeated abdominal packing. Persistent bleeding was temporarily controlled by high dose rFVIIa (fig. 1A), platelet transfusions, fibrinogen, and tranexamic acid. Inhibitor elimination as well as Factor VIII-c restitution was finally achieved on POD 100 (fig. 1B).

An enterocutaneous fistula had developed at the level of the transverse colon on POD 55. The abdominal cavity was partially open, and recurrent interenteric abscesses occurred that were accompanied by septic shock. Pathogens included *K. pneumoniae*, *M. organii*, extended spectrum  $\beta$  lactamase *E. coli*, *E. faecium*, and *P. aeruginosa*. Drainage was achieved by repeated computer tomography-guided placement of pigtail catheters under antibiotic coverage. These complications required prolonged intensive care treatment after bleeding control.

On POD 200, the patient was again extubated, did not require ventilator support, was cardiovascularly stable, received full enteral nutrition, had normal kidney function, communicated freely, and spent several hours outside the hospital with her family. However, on POD 207 she developed another episode of septicemia. Despite aggressive treatment, this resulted in septic shock with multiorgan failure as a result of panantibiotic-resistant *P. aeruginosa* on POD 216. The patient died on POD 217.

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**Table 1. Coagulation Parameters at the Time of Diagnosis**

Test	Result	Reference Range
Prothrombin Time	Quick Innovin/INR 72%/INR: 1.1	/INR: <1.2
aPTT	—	70 s
Actin PTT	—	50 s
Lupus anticoagulants	—	Negative
Factor VIII: c	Monophase test	4%
vWF: RCF	—	84%
vWF: antigen	—	90%
Factor VIII inhibitor	Bethesda test (Nijmegen protocol)	117 BU
Fibrinogen	Clauss method	3.0
Factor II, V, VII, IX, XI, XII	Monophase test	Normal range
Factor XIII	Monophase test	45%
		>70%
		>60%

aPTT = activated partial thromboplastin time; BU = Bethesda Unit; INR = international normalized ratio; PTT = partial thromboplastin time; RCF = ristocetin cofactor; vWF = von Willebrand factor.

## Discussion

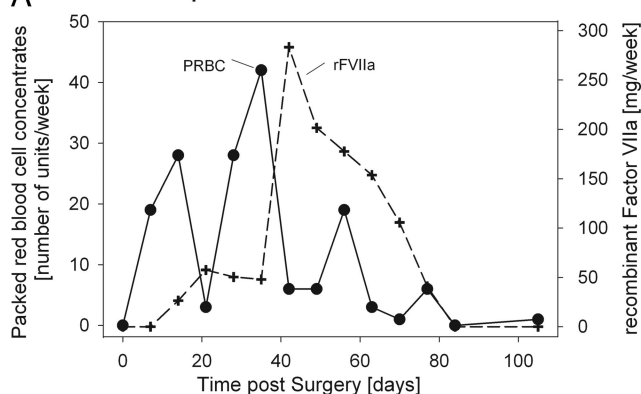
Our case report demonstrates the catastrophic consequences of performing extensive visceral surgery in a nonhemophilic patient with a newly acquired Factor VIII inhibitor and insufficient preoperative preparation. If a patient is scheduled to undergo major surgery and presents with an abnormal coagulation study, the pathologic results should be verified preoperatively. Should the repeat study generate an abnormal value, the patient should be specifically asked about signs of a bleedings disorder (e.g., soft tissue hematoma) and a coagulation expert should then be consulted.

### Patient Presentation and Demographic Characteristics

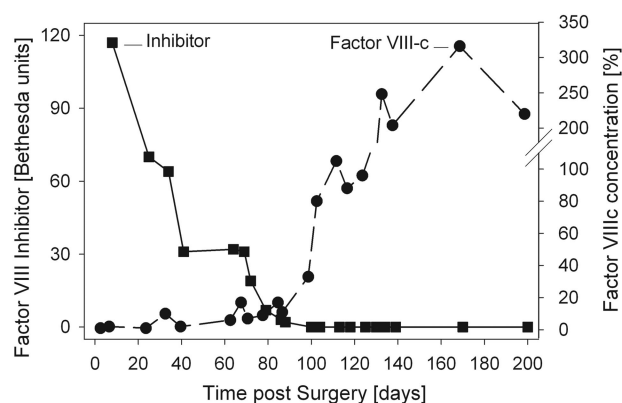
Our patient was 57-yr-old, previously healthy with no congenital hemophilia, and presented with progressively more severe postoperative bleeding. In a prospective cohort study, nonhemophilic patients with autoantibodies to coagulation factors (acquired hemophilia) were studied by the United Kingdom Hemophilia Centre Doctors' Organization.<sup>3</sup> Over a 2-yr period they identified 178 patients. Patients were mostly older than 65 yr (85%; median age 78 yr) and had no coexisting disease (63%). Acquired hemophilia was associated with malignancy (15%), autoimmune or collagen vascular disease (15%), pregnancy (2%, mostly postpartum) or dermatologic diseases (3%), and these coexisting diseases are significantly more frequent in younger patients. Spontaneous bleeding frequently occurs subcutaneously (25%), in muscle (45%), or in the gastrointestinal tract (22%). Fatal bleeding is present in 9% (gastrointestinal, intracranial, retroperitoneal, and perioperative).

\* <http://www.asahq.org/publicationsAndServices/BCTGuidesFinal.pdf>. Last accessed June 30, 2009.

### A Transfusion requirements and activated factor VII treatment



### B Factor VIII-inhibitor elimination and effect of treatment



**Fig. 1. Postoperative bleeding activity and coagulation abnormalities.** (A) The weekly transfusion requirements of packed red blood cell concentrates (PRBC; ●). Three major bleeding episodes occurred, as demonstrated by sudden rises in requirements. Furthermore, weekly doses of rFVIIa (+) are shown in parallel. (B) Factor VIII inhibitor (■) and Factor VIII coagulation activity (FVIII-c; ●) is demonstrated during the postoperative period. Treatment with steroids, rituximab, immune cells adsorption, and intravenous immunoglobulins resulted in complete and persistent inhibitor elimination by postoperative day (POD) 100.

### Establishing the Diagnosis of Acquired Hemophilia

If unexpected bleeding occurs, adequate first-line treatment should be given.<sup>#</sup> Our patient presented with diffuse bleeding and a prolonged aPTT. This can be because of factor deficiencies (VIII, IX, XI, XII, or fibrinogen), von Willebrand syndrome, lupus anticoagulants, medication effects (e.g., heparin, hirudin, activated protein C), fibrinogen split products, or acquired hemophilia with antibodies against coagulation factors (treatment-related alloantibodies in hemophilic patients or autoantibodies in nonhemophilic patients). In the case of acquired Factor VIII inhibitors as a result of autoantibodies, a decreased Factor VIII is found and the pathologic aPTT is not corrected if aPTT is determined after mixing patient and pool plasma. Other coagulation studies such as international normalized ratio and factor concentrations (fibrinogen, Factors II, IX, XI, XII, XIII, and von Willebrand factor ristocetin-cofactor and antigen, table 1) are within normal limits. Lupus anticoagulants

**Table 2. Outcome of Surgery in Patients with Unknown Acquired Factor VIII Inhibitor**

Underlying Disease	Type of Surgery	Time (Surgery to Bleeding)	Treatment of Bleeding	Outcome	Preop. aPTT (s)	Factor VIII Inhibitor (BU)	Inhibitor Elimination
Sepsis (infected hip arthroplasty) <sup>8</sup>	Girdlestone arthroplasty	None	>100 PRBC, aPCC, tranexamic acid	Hip exarticulation	45–65	n.d.	Steroids, IVIG
Posttraumatic soft tissue necrosis <sup>9</sup>	Free muscle flap	None	40 PRBC	No sequelae	32.6	50	Steroids, plasma exchange
Chronic low back pain <sup>10</sup>	Lumbar discectomy	8 days	16 PRBC, factor VIII (human), rFVIIa, tranexamic acid	No sequelae	44	9	Steroids
Lower extremity compartment <sup>11</sup>	Hematoma evacuation	None	>10 PRBC, factor VIII (human), aPCC	No sequelae	148	64	Steroids, cyclophosphamide
Upper extremity compartment <sup>12</sup>	Fasciotomy (forearm)	None	No PRBC, factor VIII	No sequelae	51	n.d.	None
Acute cholecystitis <sup>13</sup>	Open cholecystectomy	None	6 PRBC, factor VIII	Sudden death (12 h later)	n.d.	6	IVIG
“Recent” cholecystitis <sup>14</sup>	Cholecystectomy	4 days	“Multiple” PRBC, factor VIII	Recurrence of inhibitor	Normal	5	None
Abdominal pain <sup>15</sup>	Cholecystectomy	18 days	4 RBC, rFVIIa	Death (bleeding)	Normal	22.4	—
Ischemic bowel disease <sup>14</sup>	Bowel resection	4 days	“Multiple” PRBC, factor VIII	No sequelae	Normal	3.25	Steroids, IVIG, plasma exchange
Abdominal wall hernia <sup>15</sup>	Hernia repair	4 days	Unknown number of PRBC, rFVIIa	Recurrence of inhibitor	Normal	10.4	Steroids, IVIG, cyclophosphamide
Vaginal delivery with episiotomy <sup>16</sup>	Curettage, then laparotomy	6 days	Unknown number of PRBC, factor XI concentrate	Death (bleeding)	n.d.	19	Cyclophosphamide
Unruptured cerebral aneurysm <sup>17</sup>	Aneurysm clipping	7 days	No PRBC, factor VIII	Intracranial bleeding	Normal	2 BU	Steroids, cyclosporine
Retropharyngeal hemorrhage with airway obstruction <sup>18</sup>	Hematoma evacuation	None	No PRBC, rFVIIa, aPCC	Temporary tracheostomy	Ratio 2.2	67	Steroids
Dental decay <sup>19</sup>	Extraction of teeth	None	>18 PRBC, rFVIIa, aPCC, aminocaproic acid	Retroperitoneal hematoma	59	10.4 BU	Steroids, IVIG, cyclophosphamide
Cataract <sup>20</sup>	Cataract surgery	12 hours	4 PRBC, factor VIII	Loss of vision	n.d.	61	Steroids, IVIG

aPCC = activated prothrombin complex concentrate; IVIG = intravenous immune globulin; n.d. = not determined; PRBC = packed red blood cell concentrates.

are not present. Thrombocyte count and function are also normal. Factor VIII inhibitor concentrations are determined by mixing patient and control serum in a dilution curve using an enzyme-linked immunosorbent assay. One Bethesda unit describes a 50% decrease in Factor VIII activity (Nijmegen-Bethesda protocol<sup>4</sup>). Importantly, neither Factor VIII levels nor inhibitor concentrations accurately predict bleeding intensity. A Factor VIII gene analysis is not indicated, since it is an acquired disease without a genetic background.

A number of case reports describe the clinical course and outcome of surgeries in patients with acquired Factor VIII inhibitor but no accompanying congenital hemophilia A (table 2). Patients will sometimes not be identified preoperatively for several reasons (table 2). Coagulation studies can be near or even within normal limits before surgery. Alternatively, hospital policy or national guidelines do not demand these studies for minor surgical procedures, and these will thus not be available preoperatively. Mistakes can occur and surgery is performed despite abnormal values, or the risks are underestimated. However, even minor surgical procedures (e.g., insertion of central lines or extraction of teeth) can have devastating consequences in these patients (table 2). Bleeding can occur during or immediately after surgery, but often involves a time delay of several days.

#### *Treatment of Acute Bleeding*

Our patient presented with two major episodes of acute bleeding. During the first episode, diffuse bleeding was noticed on surgical reexploration and was controlled by aFVIIa by POD 14. *De novo* and massive bleeding started again on POD 29. It originated from the gastroduodenal artery and was probably a result of an erosion caused by a drainage tube. It finally was controlled by surgical ligation, abdominal packing, and rFVIIa treatment.

While patients with congenital hemophilia A are treated with Factor VIII concentrates, this is not recommended in patients with acquired hemophilia. Our patient was initially treated with fresh frozen plasma and Factor VIII concentrates. Especially Factor VIII concentrates are ineffective, and might even increase bleeding since they can boost the formation of autoantibodies. Thus, two treatment options exist that are recommended in international consensus guidelines<sup>5</sup>: aPCC (50–100 units/kg every 8–12 h with a maximum daily dose of 200 units/kg), and rFVIIa (90 µg/kg, up to every 2 h because of its short half-life). If either aPCC or rFVIIa is ineffective, the other should be tried. aPCC is an activated prothrombin complex and bypasses the necessity of Factor VIII activation. rFVIIa induces supraphysiologic concentrations of Factor VIIa, which bind to

thrombocytes and thereby directly activate Factor X and subsequently thrombin. Both aPCC and rFVIIa are very expensive, and daily treatment costs can exceed \$20,000.

Importantly, bleeding can persist for days or even weeks. Furthermore, inhibitors can reoccur after successful elimination, leading to recurring bleeding episodes. In our patient, bleeding persisted for almost 10 weeks, leading to massive transfusion requirements (fig. 1), but was finally controlled.

### *Factor VIII Inhibitor Elimination and Surgery in Patients with Known Acquired Hemophilia*

Inhibitor elimination aims to suppress autoantibody production using immunosuppressive agents. Treatment should involve steroids (prednisolone  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) with or without cyclophosphamide ( $1.5\text{--}2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) for 4–6 weeks. Rituximab is considered a second-line treatment. For high-risk patients, plasmapheresis with immune adsorption and intravenous immunoglobulin treatment with or without Factor VIII substitution has been recommended.<sup>5,6</sup> Complete remission can be achieved in 70–80% of patients, and involves a median time of 40–60 days (range, 2–360 days).<sup>3,5</sup> Since acquired hemophilia A is more frequent in older patients, it is important to note that inhibitor elimination occurs faster in older patients than in the younger age group.<sup>3</sup>

We achieved complete remission in 70 days using corticosteroids, immune adsorption, and high-dose intravenous immunoglobulins. Cyclophosphamide was not used, and only a single dose of rituximab was given because of the recurrent infectious complications.

If patients with acquired hemophilia are identified preoperatively, surgery should be postponed except for life-threatening emergencies. Prior inhibitor elimination should be seriously considered in collaboration with coagulation experts. If successful, surgery has been reported to occur without bleeding complications (e.g., lobectomy<sup>7</sup>). If surgery cannot be postponed, prophylactic treatment with FEIBA or rFVIIa should be seriously considered.

In summary, acquired hemophilia A is caused by autoantibodies (so-called inhibitors) to coagulation factors (mostly Factor VIII). Patient can be often identified by a history of unexplained bleeding episodes and by a pro-

longed aPTT. Before surgery, inhibitor elimination should be attempted. If surgery is urgent or unexpected bleeding occurs, treatment options include aPCC or rFVIIa.

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## Tube-in-tube Emergency Airway Management after a Bitten Endotracheal Tube Caused by Repetitive Transcranial Electrical Stimulation during Spinal Cord Surgery

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WE report a case of bite damage to a wire-reinforced endotracheal tube caused by transcranial electrical stimulation (TES).

A 23-yr-old female patient (American Society of Anesthesiologists grade I) with mild motor deficits in the lower extremities was admitted for the extirpation of an intramedullary cervical spinal cord tumor (C3-C7).

Intraoperative neurophysiological monitoring by using motor-evoked potentials (MEPs) elicited by TES and somatosensory-evoked potentials was performed to assess the functional integrity of the spinal cord.<sup>1</sup> After induction of general anesthesia by using bolus administration of propofol, remifentanyl, and muscle relaxation (0.6 mg/kg rocuronium), a 7.5-mm ID armoured endotracheal tube with cuff (Rüschflex; Teleflex, Kernen, Germany) was introduced, cuffed, and fixed with adhesive tape. A gauze bite block was placed in the recommended manner<sup>2</sup> to prevent bite injuries because tongue bites, lip lacerations, and even a unique case of mandibular fracture were reported during TES in patients without bite block.<sup>3</sup> Anesthesia was maintained by continuous infusion of propofol ( $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and remifentanyl ( $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). The neuromuscular blockade was omitted after induction of general anesthesia to avoid interference with MEP monitoring.

Neurosurgical access was intended from the posterior; therefore, the patient was turned to a prone position, and TES for MEP monitoring was initiated. Scalp electrodes at positions C3 and C4 were used for TES according to the International 10-20 electroencephalography electrode system.<sup>4</sup> Short trains of 5-7 electrical pulses (frequency 250 Hz, duration of each stimulus 0.5 ms, intensity 80 to 250 V) were applied *via* corkscrew electrodes originating from a Nicolet Endeavor (Viasys Healthcare, Madison, WI) constant current stimulator to monitor MEPs from limb muscles. Single stimuli of TES were used to record epidural MEPs from an intraopera-



Fig. 1. Bitten hole caused by repetitive transcranial electrical stimulation.

tively placed epidural catheter electrode.<sup>1</sup> At critical stages of the surgical procedure, short trains of stimuli were used at a rate of 1.1 Hz to continuously assess the functional integrity of motor tracts. During the entire surgical procedure, a total of 4,200 trains of stimuli were applied.

Approximately 6 h after incision, the ventilator alarmed leakage. At this point, oxygenation and ventilation could only be performed by high-flow hand ventilation with 100% oxygen. Direct inspection of the endotracheal tube with the patient remaining in prone position revealed a bitten hole near the incisors (fig. 1), although the gauze bite block was still correctly in place. In this emergency situation, a thinner, 5 mm endotracheal tube (Microcuff; Kimberly-Clark, Neenah, WI) (table 1) was inserted into the injured endotracheal tube

Table 1. A Tube-in-tube Study

Inner Tuber Inner Diameter, mm	Outer Tube Inner Diameter, mm
6.0	9.0
5.5	8.5
5.5	8.0
5.0	7.5
4.5	7.0
4.0	6.5
3.5	6.0
3.0	5.5
2.5	5.0

The best size for the inner tube (left column) corresponds to the size listed for the outer tube (right column). We tested tubes made by Teleflex and Kimberly-Clark.

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(with care not to mislead the new endotracheal tube through the perforation<sup>5</sup>), fixed using adhesive tape, and cuffed (fig. 2) without changing the patient's position. Pulmonary auscultation was normal. The gauze bite block was replaced by a rubber bite block to prevent further biting of the tube, and mechanical ventilation was continued until the end of the surgical procedure. The critical incidence did not lead to decrease in blood oxygen saturation, which constantly remained above 97%, as measured by pulse oximetry.

There were no further respiratory complications; however, because of the increased resistance of the inserted 5-mm tube, a higher peak-pressure was necessary for ventilation until extubation at the end of surgery. Post-operational inspection of the endotracheal tube revealed a 23-mm-long laceration located on the convex side of the endotracheal tube, encircling 70% of the outer circumference (fig. 1 and 2). The endotracheal tube perforation on the convex side had been under the upper incisors during the operation. After extubation in the operating room, it was found that the patient had suffered no injuries that might have occurred during the use of TES. The patient was transferred in a stable condition to the postoperative care unit.

## Discussion

Several publications have associated the use of wire-reinforced tubes with airway complications such as perforation,<sup>5,6</sup> occlusion,<sup>7</sup> obstruction,<sup>8,9</sup> or dissection.<sup>10</sup> There is only a single report of a bitten and consecutively leaking tube caused by jaw muscle contraction after TES<sup>11</sup> and a single report of tube obstruction while the patient was in prone position.<sup>12</sup> Both were managed in a different manner from our case.

Santos *et al.*<sup>12</sup> and MacDonald<sup>11</sup> reported emergency reintubation; in both cases, the patient had to be returned to the supine position. We managed this critical event without being forced to change the patient's position by introducing the thinner tube into the perforated one. We decided to do so, because ventilation could be maintained manually, thereby not justifying the high-risk option of breaking the sterile field by altering the position. With this strategy, the intramedullary spinal cord tumor could safely be removed under continual MEP monitoring.

The usual infusion rate of propofol is 25–100  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and 0.25–1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  of remifentanyl when combined with propofol for maintenance of anesthesia.<sup>13</sup> Therefore, anesthesia should have been deep enough at all times, which minimizes the possibility of the laceration being caused by the patient consciously biting the tube. This serious complication was most likely caused by the sum of repetitive strong bites as a side effect of continuous

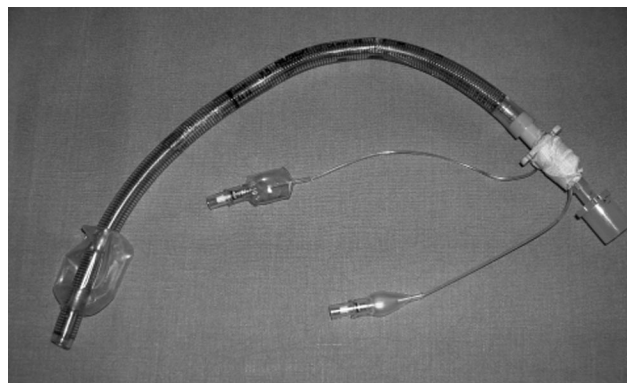


Fig. 2. Bitten reinforced tube (7.5-mm inner diameter) with the thinner tube inside (5 mm inner diameter).

MEP monitoring, rather than by a single strong bite. The duration of the surgical procedure for the removal of an intramedullary spinal cord tumor reaching from C3 to C7 required extraordinarily frequent TES to test the functional integrity of the motor pathways, which is unusual among other types of spinal surgery.

Because of the short duration of masticatory muscle contractions associated with MEPs, no pressure warning occurred at any time, indicating airway obstruction or leakage. Leakage was noted at the point when the ventilator exceeded its standard limit (more than 25% of min volume); before exceeding the limit, this value was not displayed on the main screen (Primus; Dräger Medical, Vienna, Austria). Particularly strong activation of the temporalis muscle has been reported when TES is applied *via* the C3 and C4 electrode positions because direct activation of the muscle or the motor part of the trigeminal nerve is induced by the electrical stimulus.<sup>14</sup> This can be avoided by using alternative stimulation sites of scalp electrodes, *e.g.*, C1 and C2. However, higher intensities of TES are necessary to reach motor threshold if C1 and C2 are used.<sup>15</sup>

## Conclusion

This emergency event demonstrates that the previously recommended gauze bite block cannot prevent endotracheal tube perforation for surgical procedures with the use of TES for MEP monitoring. Instead, a reliable device that provides both protection of the patient's oropharynx (tongue, teeth and lips) and protection of the endotracheal tube should be used.<sup>16</sup> Our tube in tube management could sufficiently manage this airway emergency situation in prone position. If TES is effectively accomplished *via* electrodes on positions C1 and C2, this method should be preferred over C3/C4 stimulation for MEP monitoring in spinal cord surgery.

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