Perioperative care of a child with tetanus

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Abstract

Tetanus is caused by tetanospasmin, a toxin that is produced by the anaerobic bacterium, *Clostridium tetani.* Despite widespread vaccination, which limits its incidence in many parts of the world, tetanus may still occur owing to lack of immunisation related to religious tenets, cultural beliefs or inaccessibility to medical care. Of major concern during the perioperative care of such patients is control of the muscle spasms and the propensity for autonomic dysfunction, resulting in blood pressure instability. Ongoing muscle spasms may impair upper airway control or respiratory muscle function, thereby resulting in respiratory failure. Autonomic dysfunction may result in profound hypertension followed by hypotension, bradycardia and asystole. The pathophysiology of tetanus, its clinical manifestations, and current treatment options are discussed. The preoperative implications of tetanus and the care of these patients are reviewed.

Introduction

Tetanus is caused by tetanospasmin, a toxin that is produced by the anaerobic bacterium, *Clostridium tetani.*[1] After inoculation or introduction into the soft tissue, the spores of *C. tetani* multiply and produce a toxin that acts on specific areas of the central nervous system, leading to the characteristic spasms and clinical symptoms. With appropriate immunisation or effective wound care, including administration of immunoglobulin in unimmunised patients, tetanus is rare in developed countries with ready access to medical care. However, even in developed countries there may be social or religious objections to routine immunisation. Hence tetanus remains a health hazard in various parts of the world. We report the case of an unimmunised child with tetanus who required intraoperative and perioperative care.

Case report

The patient was a six-year-old, 22.6 kg Amish child who had received no immunisations. He was previously healthy until two days prior to admission, when he developed progressive muscle spasms in his back, arms and legs, and the inability to open his mouth. Two weeks prior to presentation he had had a puncture wound in his foot from a sharp chicken bone fragment. No medical attention was sought for this injury. In the emergency department his vital signs were stable (blood pressure 121/68 mmHg, heart rate 124 beats per minute, temperature 37.2 °C) and his oxygen saturation was 100%. During the initial examination he had frequent muscle spasms of his trunk and extremities. The initial treatment included intravenous midazolam, metronidazole and tetanus immunoglobulin (3 000 units). His parents refused tetanus immunisation. The muscle spasms subsided with the intravenous midazolam and he was admitted to the Paediatric Intensive Care Unit (PICU) for ongoing observation.

Over the course of the next 12-16 hours, there was progression of the clinical signs and symptoms of tetanus, with increased muscle spasms and the onset of stridor with periods of decreased gas exchange. Treatment was initiated with intermittent doses of morphine and diazepam. When these failed to control the muscle spasms, an infusion of dexmedetomidine was started. Although this lessened the symptoms to some extent, he still had episodes of severe muscles spasms, and respiratory compromise with periodic decreases in his oxygen saturation. Given the upper airway issues and the concern that pathology other than tetanus may be causing these problems, he was transported to the operating room for flexible fibre-optic bronchoscopic examination of the airway.

With the otolaryngologist in the operating room, inhalation induction was carried out with sevoflurane in 100% oxygen. The patient's respiratory effort could be assisted without difficulty. Following the induction of anaesthesia with maintenance of spontaneous ventilation, a nasal trumpet was placed in one nostril, and the administration of sevoflurane continued (inspired concentration 4-6%) through the nasal trumpet. Flexible fibre-optic bronchoscopy was performed via the other naris while maintaining spontaneous ventilation. Prior to insertion of the bronchoscope into the nose, the bronchoscope was placed through a cuffed endotracheal tube (ETT). The upper airway and subglottic area were free of pathology. The bronchoscope was passed into the trachea and the ETT advanced over the bronchoscope into the trachea. Breath sounds and exhaled end-tidal carbon dioxide confirmed appropriate placement of the ETT.

The patient was transported to the PICU. His subsequent hospital course was significant for ongoing muscle spasms despite intravenous infusions of midazolam, morphine, and dexmedetomidine. Control of the muscle spasms was eventually achieved with neuromuscular blockade using vecuronium. A magnesium infusion was started on the first hospital day to treat intermittent bouts of autonomic dysfunction, manifested as hypertension and tachycardia. The magnesium was subsequently discontinued during an episode of hypotension. Over the first two to three days of hospitalisation, there was a progressive increase in his creatinine phosphokinase (CPK) levels, to a maximum of 10 000 units/dl, and haemoglobinuria. This was treated by maintaining an alkaline diuresis. With the institution of neuromuscular blockade, the CPK values declined. Mechanical ventilation and neuromuscular blockade were continued for a total of 12 days. Ongoing treatment for the tetanus included a 10-day course of intravenous metronidazole, a total of three doses of tetanus immunoglobulin, and removal of the chicken bone fragment from his foot. He was eventually discharged home following a 23-day hospital stay.

Discussion

Tetanus, a rare disease in developed countries, is caused by *C. tetani*. This Gram-positive bacillus is commonly present in soil, but may also be found in the gastrointestinal tracts of humans and domesticated animals.[2] Inoculation with *C. tetani* spores typically occurs through a contaminated wound. As an obligate anaerobe, the bacillus cannot grow in healthy oxygenated tissue, thus explaining the fact that tetanus-causing wounds are usually associated with co-infection, necrotic tissue, a foreign body or localised ischaemia.[3]

The tetanus bacillus produces two toxins: tetanospasmin and tetanolysin. Tetanolysin damages surrounding tissue and is also capable of haemolysis. Although tetanolysis plays no direct role in the clinical manifestations of tetanus, it is thought to optimise conditions for bacterial proliferation.[3] The clinical features of tetanus are caused by tetanospasmin (a metalloprotease). It enters the peripheral nervous system directly from the contaminated wound and is capable of affecting motor, sensory, and autonomic neurons. In approximately 20% of cases, no entry wound is noted. The incubation period (time from injury to disease manifestation) varies from one to 60 days. Tetanospasmin travels through axons in a retrograde fashion to the central nervous system (CNS). The primary pathological effect of tetanospasmin is the cleavage of synaptobrevin, which is a presynaptic protein. Synaptobrevin facilitates the fusion of neurotransmitter vesicles to nerve membranes, and the release of their contents into the synapse. By cleaving synaptobrevin, neurotransmission is effectively blocked. Radiolabelled assays have shown that tetanospasmin has a preference for inhibitory motor neurons, which explains the clinical picture of muscle rigidity.[4,5]

Tetanus may present in one of four clinical forms: local, cephalic, neonatal and generalised. Localised tetanus involves local toxin production at the site of injury, with the spastic contraction of muscles in the area. Although localised disease may occur as an isolated entity, localised tetanus often progresses to generalised tetanus. Neonatal tetanus is a form of generalised tetanus that occurs within the first 28 days of life. It generally results from contamination of the umbilical stump with the organism. Although neonatal tetanus accounts for fewer than 10% of cases, it accounts for 50% of deaths from tetanus. Cephalic tetanus is a form of localised tetanus that originates from head and neck injuries. As with localised tetanus, it also commonly progresses to the generalised form. Cephalic tetanus can produce a confusing clinical picture as it is easily confused with cranial nerve dysfunction and neuropathies.

Generalised tetanus is the most common form of the disease, as it represents 80% of all cases.[6] The first symptom frequently includes muscle spasms of the neck and jaw, hence the common colloquial term "lockjaw". Involvement of the facial musculature results in "risus sardonicus", a characteristic grinning expression produced by spasm of the facial muscles. The disease then progresses to widespread skeletal muscle contractions with intermittent, severe spasms. Although the spasms typically last for one to three weeks, rigidity may persist for four to eight weeks. The muscle spasms associated with generalised tetanus may result in extreme pain, while the disease itself causes no impairment in awareness. Hence aggressive pain management through the use of intravenous opioids and adjunctive agents is necessary in these patients. As the disease progresses, autonomic instability may develop. This initially presents as irritability and diaphoresis, with progression to profound swings in blood pressure and heart rate.

In developed countries, tetanus has all but been eliminated through immunisation. However, tetanus remains a problem in developing countries and, as our patient demonstrates, it may still occur in developed countries when immunisations are omitted for social or religious reasons. Effective immunisation requires dosing throughout the first two years of life (at ages two, four, six and 15-18 months) with other routine childhood immunisations, and then again at four to six years of age. Another dose is recommended for adolescents at 11-12 years of age, as well as a booster dose every ten years for adults.[7] During infancy, immunisation includes the DPT (diphtheria, pertussis, and tetanus toxoid), while in most circumstances the tetanus toxoid is combined with immunisation against diphtheria for adults (Td) when the periodic booster is administered (every 10 years).

After appropriately completing a tetanus immunisation series, the majority of recipients have antibody levels that exceed the minimum protective level. Although no randomised trial has ever been conducted, it has been inferred that the efficacy of a protective antibody level approaches 100%. Because antibody levels decline over time, a booster vaccination is recommended every 10 years. However, in a small percentage of persons, antibody levels may dip below a protective level before 10 years. For this reason, a booster is recommended in the presence of a dirty wound that occurs at a time greater than five years from the last booster.

Although treatment is primarily preventative, sporadic cases of clinical tetanus still occur. Treatment of clinical tetanus must be guided primarily by case reports, as very few randomised trials have been conducted investigating therapeutic strategies for tetanus. As illustrated by our patient, treatment includes halting further toxin production, neutralising circulating toxin and controlling the clinical manifestations induced by the toxin that has already gained access to the CNS. Halting toxin production is vital to effective therapy. It is accomplished by thorough wound debridement and antimicrobial therapy with an agent that is effective against *C. tetani*. Current recommendations include the administration of intravenous metronidazole.[8] It has been suggested that penicillin, although effective in eradicating the organism, may increase mortality owing to the effects of the γ-aminobutyric acid-like structure of penicillin that has an excitatory effect on the CNS. Hence it may potentiate the effects of tetanospasmin.

Human tetanus immunoglobulin (HTIG) is used to neutralise circulating toxin. HTIG only neutralises unbound toxin and therefore does not reverse the clinical manifestations of the disease. The treatment of toxin that has already found binding sites in the central nervous system is purely supportive. Although a single intramuscular dose of 3 000-6 000 units is generally recommended, doses as low as 500 units have been effective. While some authors suggest an additional intrathecal dose of HTIG,[9] consensus in the literature is lacking and the drug is not licensed for intrathecal use. Similarly, the efficacy of wound infiltration with HTIG has not been proven. Human intravenous immunoglobulin (IVIG) contains 4-90 units/ml of HTIG and may be substituted in the absence of pure HTIG. In developing countries, equine-derived tetanus antitoxin (TAT) may be the only available option. TAT should only be administered after appropriate testing for sensitivity, as 15-20% of patients will experience serum sickness or true anaphylactic reactions to the foreign protein. Human-derived preparations are preferred because of their lack of immunoreactivity. Unlike other bacterial diseases, infection with *C. tetani* does not confer immunity. Administration of tetanus toxoid is recommended and can be done at any time during acute treatment.

As noted in our patient, stridor is a common presenting symptom related to repetitive tetanic contractures of the pharyngeal and laryngeal musculature. Given the potential need for endotracheal intubation, mechanical ventilation, neuromuscular blockade and sedation, ICU physicians and anaesthesiologists remain instrumental in the care of these patients. The initial reports of the use of neuromuscular blockade and mechanical ventilation that appeared in the 1950s followed experience gained from using these techniques during the poliomyelitis epidemics.[10] Prior to the use of these techniques, respiratory failure from the muscle paroxysms was the primary cause of death from tetanus.

The major goals in the symptomatic care of tetanus include reducing muscle spasms, controlling ventilation and managing the haemodynamic instability. Death is generally the result of respiratory failure or autonomic dysfunction resulting in haemodynamic instability. Respiratory failure requiring controlled ventilation may result from rigidity of the abdominal and chest wall musculature or diaphragmatic involvement. Paroxysms, as noted in our patient, of the upper airway (pharynx and larynx) may result in upper airway obstruction. In patients with tetanus the airway should be secured early in the management to prevent respiratory failure, and avoid hypoxia and its complications. As the need for airway control and mechanical ventilation may be prolonged, early tracheostomy should be considered, depending on the experience of the PICU staff and the medical centre in which the patient receives care.

Severe paroxysms of large muscle groups may result in rhabdomyolysis and renal failure. Periodic monitoring of the urine for the presence of myoglobin is suggested. This can be readily accomplished by bedside dipstick testing of the urine for the presence of haem or blood. Haem-positive urine without red blood cells on the microscopic examination suggests the presence of myoglobin. Maintenance of an adequate diuresis (in excess of 2 ml/kg/hour) with alkalinisation (pH over 6.6-7.0) may prevent renal dysfunction. Periodic monitoring of CPK values may be useful as elevated levels suggest impending myoglobinuria. Daily measurement of renal function (blood urea nitrogen

and creatinine) in addition to close observation of urine output is suggested. As illustrated by our patient, progressive increases in the CPK value may be indicative of inadequate control of the muscle spasms and the need to further escalate therapy.

The time-honoured therapy for the control of muscle spasms involves sedation and a dark, quiet room. The primary choice of sedative agent for the control of muscle spasms has traditionally been the benzodiazepines, and more recently midazolam.[11] In adults, doses of diazepam as high as 480 mg/day have been used while continuous infusions of midazolam up to 20 mg/hour may be needed for adequate control of muscle spasms. Although the benzodiazepines remain the primary sedative agent in use, variable success has been reported with other agents including ketamine, barbiturates, opioids and propofol.[12-15] Sedation with propofol infusion has been reported to control muscle spasms without the need for neuromuscular blocker agents.[15] However, given the potential adverse effects of propofol, including propofol infusion syndrome, such therapy cannot be recommended.[16-20] In addition to continuous infusions of sedatives to prevent spontaneous muscle spasms, pretreatment with supplemental doses may be necessary prior to nursing care and procedures to avoid triggering paroxysms.

Dexmedetomidine, a centrally acting α_2-adrenergic agonist, has found increased applications in various scenarios in the paediatric population as a result of its unique ability to render patients in a sedated yet cooperative state, with a limited risk of adverse respiratory or haemodynamic effects.[20] Given its unique central mechanism of action, resulting not only in sedation but also sympatholysis, it may not only provide sedation while preventing muscle spasms, but also aid in controlling the autonomic instability of tetanus.[21] Hence it may offer an additional agent which may be an effective adjunct to other therapies, including opioids to control pain and benzodiazepines to control muscle spasms.

Girgin et al reported preliminary experience with the adjunctive use of a dexmedetomidine infusion in six adults with tetanus.[22] Although dexmedetomidine did not completely control the paroxysms, it did reduce their frequency and severity, as well as the need for sedative, analgesic and neuromuscular blocking agents. In our patient, treatment was initiated with intermittent doses of morphine and diazepam, which failed to control the muscle spasms effectively, and therefore a dexmedetomidine infusion was started. Although this lessened his symptoms, there were still episodes that resulted in respiratory compromise and eventually necessitated endotracheal intubation. Following endotracheal intubation, continuous infusions of both midazolam and dexmedetomidine failed to control totally the muscle paroxysms, as evidenced by a continued increase in the plasma CPK concentration and the eventual need for neuromuscular blockade.

Nonsedative agents used to relieve muscle spasms include anticonvulsants, baclofen, dantrolene, and magensium.[23-26] In some cases, agents such as magnesium may be effective in not only controlling the muscle spasms, but also the autonomic dysfunction. Although magnesium has not been shown to reduce the need for mechanical ventilation, there was a reduction in the requirement for medications used for muscle spasms and cardiovascular instability.[24] Baclofen has even been given via the intrathecal route with effective control of muscle spasms, although it does carry a significant risk of respiratory depression.[26]

As noted in our patient, when pharmacological therapy of muscle spasms fails, endotracheal intubation and mechanical ventilation may be necessary. Although the skeletal muscles involved in tetanus will relax with neuromuscular blocking agents, various factors may complicate airway management. Increased intra-abdominal pressure, nonfasted state and altered gastrointestinal motility may place these patients at risk for aspiration, thereby mandating the need for rapid sequence techniques for endotracheal intubation. Although the response to depolarising and nondepolarising neuromuscular blockade is normal in tetanus,[27] the risk-benefit ratio of succinylcholine must be seriously considered given the potential for hyperkalaemia and rhabdomyolysis in patients with neuromuscular disorders.[28] Although anecdotal experience has been reported with the use of intramuscular succinylcholine without complications for the treatment of tetanus,[29] hyperkalaemia and cardiac arrest after succinylcholine administration late in the course of tetanus has also been reported.[30] Given its rapid onset, compared with other agents, rocuronium appears to be a logical choice for initial airway management and rapid sequence intubation. Although it has been used effectively in patients with tetanus, pancuronium carries the theoretical risk of increased adrenergic activity. The choice for long-term neuromuscular blockade includes any of a number of the nondepolarising neuromuscular blocking agents. As with other disease processes, when such therapy is used there may be a risk of myopathy of critical illness, with prolonged postrecovery issues.[31] Following endotracheal intubation, restrictive-like problems with mechanical ventilation may result from chest wall rigidity secondary to involvement of the intercostal and abdominal musculature, thereby necessitating ongoing neuromuscular blockade. Additional respiratory involvement may include bronchospasm and bronchial hypersecretion.

One of the other primary goals in the therapy of tetanus is control of the autonomic instability. The impact on survival cannot be denied as autonomic instability remains a common cause of mortality later in the disease process.[32] Episodic and extreme hypertension and tachycardia have been termed "autonomic storms". These may occur without an identifiable precipitating event. The pathophysiology behind the autonomic storms is an elevated level of basal norepinephrine with periodic spikes in the plasma

epinephrine concentration.[33] The plasma levels of epinephrine may be 100 times the normal limit, similar to those seen with a phaeochromoctyoma. Autonomic storms may be followed by profound, therapy-resistant hypotension, bradycardia, and asystole. The parasympathetic nervous system may also be involved as acetylcholine excess may also be involved in the autonomic dysregulation.[34] Dolar reported the successful use of atropine infusions in four adults with tetanus.[34] With therapy, the patients maintained complete cardiovascular stability. Furthermore, signs of respiratory involvement including bronchospasm, bronchial hypersecretion and hypersalivation were absent.

Autonomic dysfunction and hypertensive crises have been treated with a variety of pharmacological agents, including β-adrenergic antagonists (phentolamine), direct-acting vasodilators including sodium nitroprusside, calcium-channel antagonists, and mixed α- and β-adrenergic antagonists (labetalol). In general, short-acting agents are suggested to avoid excessive hypotension between crises; however, there are limited data regarding the use of titratable intravenous vasodilators such as nitroglycerin and sodium nitroprusside. Propranolol and other β-adrenergic antagonists are not recommended, owing to the risk of morbidity and even mortality from unopposed β-adrenergic activity. Anecdotal success has been reported with the α_2-adrenergic agonists clonidine and dexmedetomidine.[21,22] Direct-acting vasodilators of the dihydropyridine class of calcium-channel antagonists, such as nicardipine, have also been used to control hypertension in patients with tetanus. However, given its duration of action, excessive hypotension may occur. Although there are no reports of its use in patients with tetanus, clevidipine (a dihydropyridine calcium-channel antagonist) offers the theoretical advantage of rapid blood pressure control with a short duration of action, given its metabolism by plasma esterases.

Owing to its multiple pharmacological actions, magnesium sulphate may act directly to treat both muscle spasms and autonomic instability. Muscle spasms are relieved by blockade of the inward movement of calcium into presynaptic channels and a decrease of acetylcholine release. Magnesium has also been shown to be effective in controlling the autonomic instability associated with tetanus.[35] Adverse effects include skeletal muscle weakness and respiratory failure, which mandate periodic measurement of serum concentrations. Furthermore, as noted in our patient, vasodilatation may result in hypotension, although this is uncommon in the absence of hypovolaemia.

The infusion of local anaesthetic into the epidural or intrathecal space is yet another option for controlling autonomic instability as well as alleviating muscle spasms. Anecdotal reports and small case series have shown that epidural and spinal bupivacaine have resulted in improved cardiovascular stability, although hypotension from the sympathectomy may require treatment.[36,37] The neuraxial anaesthetic technique has the benefit of producing a regional sympathectomy, controlling autonomic dysfunction, as well as providing analgesia for painful muscle spasms.

To date, there are limited reports regarding the anaesthetic care of patients with acute tetanus.[38,39] Surgical procedures are occasionally required in patients with tetanus, including wound debridement or tracheostomy. In our patient, a thorough upper airway examination by otolaryngology was needed, and this procedure mandated a general anaesthetic. As mentioned previously, because of increased abdominal pressure, gastric stasis and involvement of laryngeal muscles, aspiration is of significant concern and would mandate the use of rapid sequence intubation. Besides the avoidance of the use of succinylcholine, because of the risk of hyperkalaemia, anecdotal evidence suggests that depolarising and nondepolarising neuromuscular blocking agents are able to provide adequate muscle relaxation in the setting of tetanus. Our patient's presentation with intermittent upper airway obstruction and stridor suggested that there may have been secondary pathology of the upper airway, thereby mandating an approach that would maintain spontaneous ventilation. Given these concerns, airway management was accomplished in the operating room with assistance from otolaryngology. Furthermore, preparation for a potentially difficult airway was in place, and spontaneous ventilation was maintained by the induction of anaesthesia with sevoflurane in 100% oxygen.

When general anaesthesia is used, a deep level of anaesthesia is suggested to avoid triggering hypertensive crises and spasms during the procedure. Various intravenous and inhalation anaesthetic agents have been used without incidence in tetanus patients. In our patient, a deep plane of anaesthesia with sevoflurane was well tolerated, and effectively controlled the clinical signs and symptoms of tetanus. We noted no intraoperative problems with muscle rigidity or autonomic dysfunction. When indicated, regional anaesthesia may be an option to provide surgical anaesthesia or combined with general anaesthesia, to limit intraoperative anaesthetic needs and provide postoperative analgesia. We have previously reported the use of spinal anaesthesia for wound debridement in a patient with tetanus who was not tracheally intubated.[38]

Conclusion

In summary, we present the perioperative care of a six-year-old patient who presented with generalised tetanus. The ICU care of such patients requires halting further toxin production, neutralisation of circulating toxin and control of the clinical manifestations induced by the toxin that has already gained access to the CNS. The basic tenets of anaesthetic care in a patient with tetanus include consideration of the implications of a full stomach, prevention of the paroxysms of muscle spasms by maintaining a deep

plane of anaesthesia or the use of regional anaesthesia, and control of the autonomic instability. As the autonomic instability may be life-threatening, invasive arterial blood pressure monitoring may be indicated. Although uncommon, with prolonged tetanus an associated cardiomyopathy from repeated exposure to catecholamines may be present. A preoperative assessment of renal and electrolyte balance may be required in the presence of myoglobinuria and renal dysfunction.

Declarations

The authors declare no financial or personal conflict. Approval for the retrospective review of this case and presentation of the material in this format was obtained from the Institutional Review Board of the Nationwide Children's Hospital, Columbus, Ohio.

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