

**CASE REPORT**

# Botulinum toxin type A treatment for a parotid gland injury in two adult horses

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## Summary

The most common disorder affecting the salivary glands in horses is trauma to the parotid gland or duct. Several management techniques have been described, each with their own set of complications. The objective of this case report was to describe the direct injection of botulinum toxin type A into the parotid gland and its outcome in two clinical cases involving damage to either the parotid salivary gland or its duct. Both cases involved iatrogenic damage to either the parotid salivary gland or its duct. Treatment for both cases involved the injection of 200 units of botulinum toxin type A into the parotid gland in order to reduce salivary production and to prevent the potential development of a chronic fistula. Follow-up assessment after the treatment was conducted via telephone consultation and photographs from the owners. In both clinical cases, a marked reduction in saliva production from the parotid gland was noted within 2 days after toxin injection and the wounds healed without complication. In the first case, the treatment was repeated after 3 weeks. No short- or long-term side effects after injection were reported by the owners. Limitations were the small number of cases and the lack of literature regarding the dose and treatment regime for botulinum toxin type A in horses. It was concluded that the administration of botulinum toxin type A appears to be a safe and effective therapeutic alternative or complementary procedure for the treatment and prevention of parotid gland or duct fistulas in horses.

## KEYWORDS

horse, botulinum toxin, duct, fistula, parotid, saliva

## INTRODUCTION

The equine salivary system comprises three pairs of glands: the parotid, mandibular, and sublingual, with the nature of the saliva produced dependent on the distribution of serous and mucous cells within the gland (Auer & Stick, 2018). The parotid gland, which is the largest, can produce up to 12L of saliva per day. It is located between the vertical ramus of the mandible and the wing of the atlas, within the retromandibular fossa. The medial aspect is intricately associated with vital nervous and vascular structures (Ashdown & Done, 2011).

The glandular secretions, which are mostly serous in nature, are conveyed through numerous small ducts, converging on the rostro-ventral aspect of the gland. This culminates in the formation of the singular parotid duct, known as Stensen's duct (Auer & Stick, 2018). This duct, initially courses along the medial surface of the caudal mandible, closely accompanying the facial artery and vein. As it ascends, the duct follows the rostral border of the masseter muscle and ultimately opens into the buccal vestibule at the parotid papilla, situated between the third and fourth maxillary premolar (Schumacher & Schumacher, 1995).

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The most common disorder affecting the salivary glands in horses is trauma to the parotid gland or duct. Due to their superficial location, these structures are particularly prone to traumatic or iatrogenic injury, with the latter occurring during surgical procedures involving the orofacial region (Dessy et al., 2007; Dixon et al., 2008; Laskawi et al., 2013; Schumacher & Schumacher, 1995). Often, the damage evades immediate detection intraoperatively but becomes apparent postoperatively as evidenced by the outflow of saliva through the surgical incision. This is because horses produce saliva only when stretch receptors in the mouth are activated by chewing or by stimulation of the oral tissues (Alexander, 1970; Dixon et al., 2008; Moeller et al., 2008). Postoperative salivary leakage results in a failure of healing and may lead to the development of a chronic fistula (Dessy et al., 2007).

Different approaches to resolve parotid fistulas, both conservative and surgical, have been described in the human and equine literature (Alexander, 1970; Dessy et al., 2007; Laskawi et al., 2013; Moeller et al., 2008). The surgical options described in horses focus on suturing the glandular defect or repairing the lacerated salivary duct with or without the use of a stent (Lempe et al., 2012; Vos & Vos, 2007). Conservative treatments focus on chemical ablation of the parotid gland, using different irritant substances such as silver nitrate, chlorhexidine or formalin, with formalin being the most effective (Auer & Stick, 2018; Williams & Nickels, 2020). In comparison to chemical ablation, surgical treatment appears to have less complications, however, it is not always technically possible (Dixon et al., 2008).

Botulinum toxin is a potent molecule produced by the bacterium *Clostridium botulinum* and exists in eight immunologically distinct serotypes designated by letters A through G and X. Botulinum toxin type A is a novel treatment used in human medicine to reduce the production of saliva by the parotid salivary gland (Dessy et al., 2007). It has been used as a treatment for salivary duct and salivary gland fistulas and hypersalivation. It has also been used for sialadenitis since the inhibition of saliva production, secondarily relieves the obstructive symptoms of pain and inflammation of the gland (Bernardo et al., 2019; Ellies et al., 2004; Strohl et al., 2021). The mechanism of action involves the inhibition of acetylcholine release at the pre-synaptic nerve terminals. This results in an irreversible neuronal blockade, affecting both motor nerves and autonomic cholinergic fibres. By disrupting the signalling cascade that mediates autonomic functions, saliva production is reduced (Ellies et al., 2004). The effect usually lasts between 4 and 6 months depending predominantly on the dose administered (Ellies et al., 2004). This reversible effect is attributed to the body's ability to regenerate the affected nerve terminals (Šoštarić et al., 2022).

Botulinum toxin type A has been used as a therapeutic intervention in various domestic species. In dogs and cats, it has been used as an antispasmodic agent whilst in horses, botulinum toxin has been investigated for the treatment of stringhalt and laminitis (Carter et al., 2009; Rogatko et al., 2016; Wijnberg et al., 2009). Additionally, in mares, botulinum toxin type B has been utilised to reduce anal

sphincter tone, with the aim of preventing incisional dehiscence following the repair of a perineal laceration. In this latter study, a horse treated with the highest dose of botulinum toxin (2500 U), had side effects such as lethargy, generalised weakness, and dysphagia (Adam-Castrillo et al., 2004).

To the best of our knowledge, the treatment of a parotid gland or duct fistula with botulinum toxin type A in horses has not been previously documented. However, based on its demonstrated efficacy in people and the low incidence of side effects, we proposed that by decreasing saliva production, it will facilitate wound healing, and thereby prevent the formation of a chronic fistula.

In this short case series, we describe the successful application of botulin toxin type A in the treatment of iatrogenic parotid gland or duct laceration in two horses.

## CASE DESCRIPTION

### Case 1

#### History

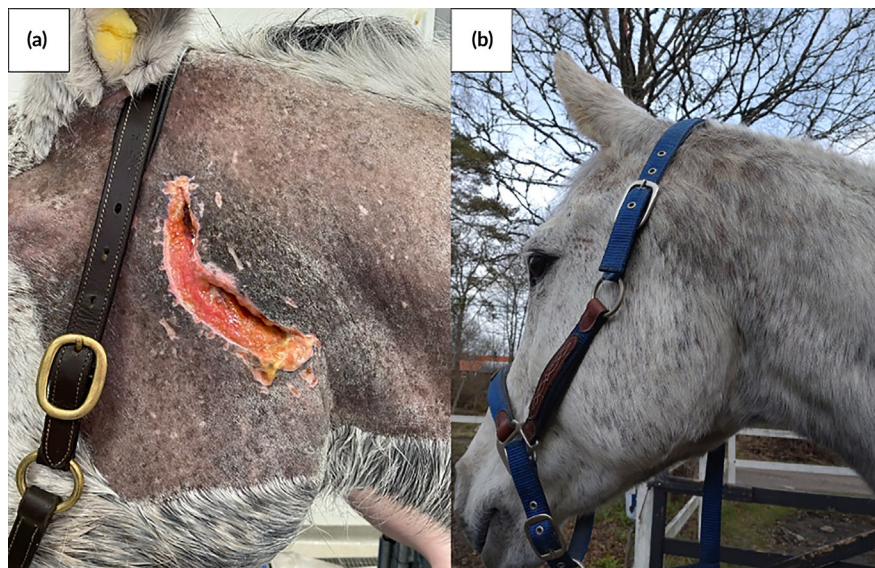
A 14-year-old, 540 kg Swedish Warmblood gelding was referred to our hospital for the removal of a large multilobulated mass, later identified as a melanoma, in the left parotid region. The horse presented in good general condition with normal vital parameters. The procedure was performed under general anaesthesia, during which the neoplasia was excised, a suction drain placed, and the wound closed.

Unfortunately, in the post-operative period, the horse developed a pronounced swelling around the wound, necessitating a second surgery procedure after 6 days. At surgery, a large haematoma was found and evacuated. Following the second intervention, however, a large volume of fluid was produced, approximately 200 mL every 3–4 h, as measured with an active suction drain.

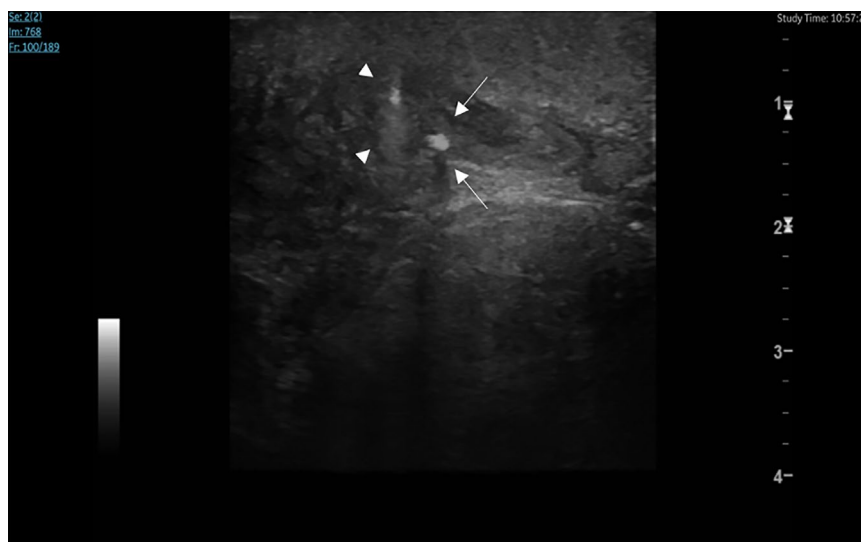
After 4 days, complete dehiscence of the wound occurred and a serous, viscous and foamy fluid emanated, which clearly increased in production when the horse was eating. The wound did not show signs of infection, and secondary healing with healthy granulation tissue commenced within a few days. However, continuous saliva leakage impeded the normal wound-healing process (Figure 1).

#### Procedure

Based on the clinical signs, we hypothesised that injury to the parotid gland was the underlying cause for the continuous saliva leakage and impaired healing of the wound. As an alternative to attempting closure of the defect or resorting to chemical ablation of the gland, we elected to administer botulinum toxin type A to reduce saliva flow and hopefully allow the parotid capsule to heal. This was the sole treatment used in both cases.



**FIGURE 1** (a) Case 1 after suture dehiscence, 4 days following the second surgical procedure and before botulinum toxin type A injection. (b) The same wound completely healed 6 weeks after the first injection.



**FIGURE 2** Ultrasound image of the parotid salivary gland in Case 1 during botulinum toxin A injection. A hyperechoic area can be seen (arrows) representing the injected botulinum toxin type A. The acoustic shadow (arrowheads) belonging to the needle can also be observed.

The horse underwent treatment, injecting a total of 200IU of botulinum toxin type A (botulinum toxin type A, purified neurotoxin complex, 100IU, Allergan®).

The procedure was performed under standing sedation using intravenous boluses, 0.01 mg/kg bwt of detomidine (Domosedan®) and 0.01 mg/kg bwt of butorphanol (Butamidior®). Prior to the procedure, 1.1 mg/kg bwt i.v. flunixin meglumine (Finadyne®), was administered as a pre-medication agent.

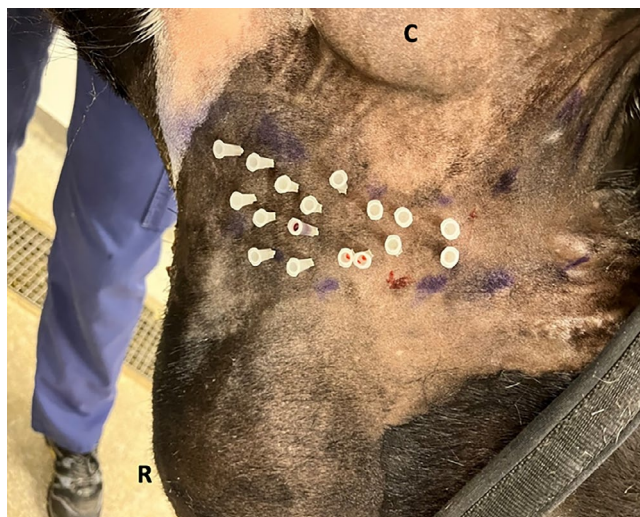
The surgical area was clipped, from the lateral canthus of the eye to 5 cm caudal to the wing of the atlas, and from the commencement of the mane to 5 cm ventral to the linguofacial vein, and aseptically prepared. An inverted L-block was performed using 15 mL of mepivacaine (20 mg/mL Carbocain®). Prior to injection, under ultrasound guidance, the depth of the parotid gland was measured and its outline

was marked with a sterile pen by an ECVDI diplomate, to help in the distribution of the injections. Following this, 200 units of botulinum toxin type A were diluted with 4.0 mL of sterile saline (9 mg/mL Braun®), yielding 5.0U for each 0.1 mL. The gland was directly infiltrated with 20 microinjections of 0.2 mL each using a 19 mm 27-gauge needle. This was performed under ultrasound guidance, to ensure that the deep glandular capsule was not penetrated (Figures 2 and 3).

### Post-operative treatment and outcome

The horse received daily medication with 1.1 mg/kg bwt i.v. Flunixin Meglumine (Finadyne®) until discharge from the hospital. Two days after the procedure, a notable decrease in saliva production from the





**FIGURE 3** Case 2: Distribution of the 27-gauge needles during direct infiltration of botulinum toxin type A in the parotid salivary gland. The outline of the parotid gland has been marked with a sterile pen (in purple). For orientation, the atlas is marked with a C (caudal) and the horizontal ramus of the mandible is marked with an R (rostral).

parotid gland was observed, along with a clear progression in wound healing. The horse was discharged from the clinic after 3 days, with no complications seen following the injection. The horse was discharged with instructions to monitor both the wound and injection sites for any signs of swelling, exudate, or pain. No medication was prescribed and daily cleaning of the wound was recommended.

The horse presented for a follow-up appointment 23 days after the botulinum toxin injection, demonstrating significant progress in wound healing, although a small amount of leakage persisted during feeding. Consequently, a second botulinum toxin injection was administered, employing the same dosage and protocol as before.

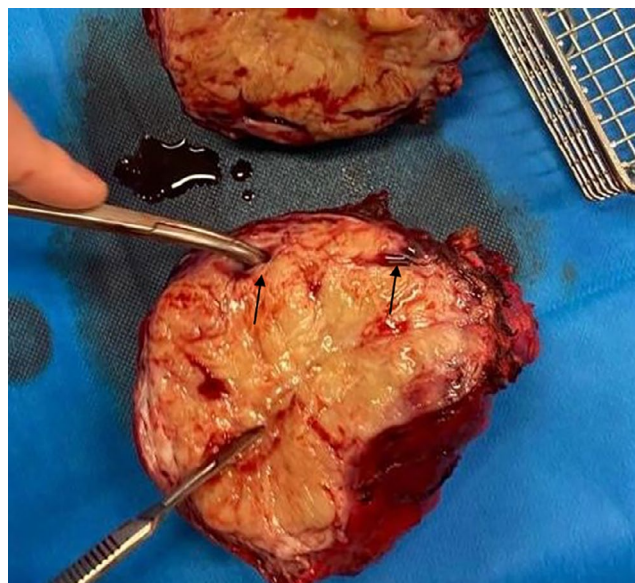
After the second injection, follow-up was conducted via telephone with the owner, who reported that saliva production decreased completely within 6 days after the second injection, and complete wound healing was observed within 6 weeks. No side effects, such as inflammation or pain in the area, were observed by the owner more than 1 year after treatment.

## Case 2

### History

An 18-year-old, 571 kg Irish Cob horse gelding was referred due to the rapid growth of a mass, later identified as a tubular adenocarcinoma, at the medial aspect of the right mandible. The horse presented in good general condition, with normal vital parameters and no difficulty in breathing or eating. Considering the rapid growth of the mass, a decision was made to proceed with surgical excision.

The surgical intervention took place under general anaesthesia, during which the mass was meticulously resected using a combination of diathermy and blunt dissection. Large blood vessels penetrating the



**FIGURE 4** Tubular adenocarcinoma removed in the area of the parotid salivary gland in Case 2 in which the parotid gland duct can be seen enclosed within the tumour. The arrows indicate the portion of the duct which was enclosed by the mass.

mass were ligated. It was suspected that the parotid duct was involved in the mass (Figure 4), however, no salivary leakage was observed during the procedure. Due to the large dead space created after the removal of the mass, the incision was left open, allowing it to heal by second intention. In the immediate post-operative period, a significant amount of bleeding was evident and could not be stemmed with packing and pressure. The horse was anaesthetised once more and the bleeding vessels ligated. The cavity was packed with gauze bandage impregnated with Polyhexamethylene Biguanide (Kerlix™ AMD).

Post-operatively, the wound exhibited a moderate level of sup-puration, characterised by the presence of serous fluid. The wound was massaged several times a day to encourage drainage. However, on the fifth day after surgery, a notable quantity of a serous, sticky and foamy fluid, which increased in production when the horse ate, gave a clear indication that the parotid duct had been iatrogenically damaged during the surgery. Since this would likely impair and slow wound healing and could lead to the development of a fistula, the decision was made to decrease saliva production by injecting botulinum toxin into the parotid gland.

### Procedure

The injection of botulinum toxin A in this case mirrored that of Case 1, using identical doses and following the same protocol.

### Post-operative treatment and outcome

The horse received for an additional day 1.1 mg/kg bwt i.v. flunixin meglumine (Finadyne®) and was discharged from the hospital the

day following the procedure. Subsequent follow-up was conducted via telephone communication and photographic documentation, revealing a clear reduction in saliva production in the week following the injection and complete healing of the wound after 21 days. No complications were reported; the only long-term behaviour change mentioned by the owner was that the horse was eating slower than before the injection but with no difficulty in swallowing. The horse showed no other side effects more than 1 year following the procedure (Figure 5).

## DISCUSSION

As stated in the introduction, damage to the parotid gland or duct can occur iatrogenically during surgery or as a result of traumatic injury. Whilst minor damage to the gland or duct may heal on its own, persistent leakage can impede wound healing and contribute to the formation of a permanent fistula (Auer & Stick, 2018). In the two cases presented in this article, the injection of botulinum toxin A led to a significant reduction in saliva production, effectively halting the leakage and resulting in complete wound healing. This outcome lays the groundwork for a novel treatment approach for the prevention and management of chronic fistulas.

Primary closure following damage to the parotid gland, or its duct should be considered the optimal treatment, since one of the main complications observed in both humans and horses, when left to heal by secondary intention, is the formation of a chronic fistula (Auer & Stick, 2018; Dixon et al., 2008). This is related to the alkaline pH of saliva, which acts as an irritant in the wound-healing process in combination with the continuous flow of saliva (Moeller et al., 2008). Surgical techniques described in horses include primary repair of the parotid duct with or without a stent, closure of a parotid

gland defect or the removal of the gland (Lempe et al., 2012; Vos & Vos, 2007). In limited case reports, parotid duct repair has shown favourable results in horses, however, stent implantation or direct repair of the duct may pose technical difficulties or lack feasibility in certain cases. Dehiscence of the surgical repair is one of the most common complications, due to continued saliva production (Lempe et al., 2012; Vos & Vos, 2007). Therefore, using botulinum toxin to temporarily reduce production could be a valuable option to help decrease this risk. As an alternative to surgery, it is possible to chemically ablate the salivary gland, for example with formalin (Schmotzer et al., 1991). This approach, which induces a permanent atrophy of the gland, is painful and may lead to abscess formation (Williams & Nickels, 2020). In addition, Jackson et al. reported that loss of function of the parotid salivary gland may have an adverse effect on the dental health of horses and should be regarded as a potential side effect to be taken into consideration (Dixon et al., 2008; Jackson et al., 2021).

In this case report, botulinum toxin was used in acute wounds only, however in the human literature, the toxin is used to treat chronic fistulas of the parotid gland. It is a well-established technique and it is considered a safe procedure, with no serious side effects reported. Therefore, this treatment emerges as a potentially safe and effective treatment for both acute wounds and chronic fistulas in horses (Eleopra et al., 2020; Ellies et al., 2002, 2004; Lawson et al., 2012).

In contrast with humans and other species, horses are very sensitive to botulinum toxin; however recent publications have shown no significant side effects following therapeutic injections of Botulinum toxin type A and B at a range of 100–300U (Carter & Ben Renfro, 2009; Wijnberg et al., 2009). There is a single publication that reported clinical signs of botulinum toxicity, such as lethargy, generalised weakness and dysphagia. However, this was at an extremely high dose of 2500U (Adam-Castrillo et al., 2004). This supports the findings in this case series, where no adverse reactions were observed. The absence of major clinical side effects of the botulinum toxin is likely attributed to the conservative dose employed and the limited diffusion of the toxin when it is injected locally (Whitlock & Buckley, 1997). These results suggest that botulinum toxin at the lower dose range of 100–300U is safe in horses. However, clinical research on the pharmacokinetics and pharmacodynamics of botulinum toxin in horses is necessary in order to establish a safe dose range.

The only mild potential side effect observed in this case series was a possible bradyphagia, exhibited by prolonged swallowing time (Case 2). This may have been the result of saliva reduction, causing the bolus to take longer to form and a delayed oropharyngeal phase of deglutition. This is consistent with the human literature, where dry mouth is a common side effect after injection of the parotid gland with botulinum toxin (Lawson et al., 2012). Since this behaviour persisted long after the proposed duration of botulinum toxin, it could also have been due to the fact that the duct was not repaired at surgery, resulting in a permanent obstruction. One potential risk of the procedure is the inadvertent injection into adjacent or deeper structures surrounding the parotid gland.



**FIGURE 5** Case 2 8 weeks after injection of botulinum toxin type A into the parotid gland. Complete healing of the wound observed.

Therefore, as performed in this case series, it is crucial to utilise ultrasound to precisely delineate the depth and boundaries of the parotid gland.

There are several reasons why the procedure needed to be repeated in Case 1. Too low an initial dosage administered could be a contributing factor, given the absence of prior literature on botulinum toxin dosage for horses. Alternative explanations include technical errors, such as imprecise ultrasound-guided administration or inaccuracy in dilution. The dose used in this study (200IU of botulinum toxin type A) was based on the efficacy in treating a similar condition in people and that used in dogs and cats as an antispasmodic agent and was regardless of the horse's body weight (Dessy et al., 2007; Rogatko et al., 2016). In other equine procedures, far higher doses have been employed, highlighting the need for further research to determine the optimal dose and application protocol, as well as to investigate the effects of botulinum toxin in additional clinical cases (Adam-Castrillo et al., 2004; Carter et al., 2009; Wijnberg et al., 2009). One of the main limitations of this case series is the absence of control, preventing confirmation of whether the wounds healed as a result of the botulinum toxin injection or whether they healed spontaneously. To address this limitation, two studies need to be conducted: the first measuring reduction in saliva production following botulinum toxin injection and its duration of action, and the second performing a case-control study following iatrogenic trauma to the parotid duct or gland.

Botulinum toxins now play a significant role in the management of a wide variety of medical conditions in people, in particular strabismus and focal dystonias, hemifacial spasm, and various spastic movement disorders (Charles, 2004; Fernández-Núñez et al., 2019; Multani et al., 2019). Of particular interest is the successful use of botulinum toxin for 'dynamic equinus foot' in patients with cerebral palsy, associated with spasticity of the gastrocnemius and gastrosoleus muscle (Cobeljic et al., 2009; Horsch et al., 2022). This suggests a potential application for flexural contraction disorders in foals, which would warrant investigation.

In conclusion, based on this small case series, the use of botulinum toxin type A for the treatment of parotid gland or duct wound and fistulas appears to be a safe and effective therapeutic alternative or complementary procedure. This approach may prove particularly valuable in cases where surgical intervention is not feasible. Further research is now necessary to further define the correct dose and treatment regime.

## AUTHOR CONTRIBUTIONS

**C. Jimenez:** Writing – original draft; conceptualization; investigation; visualization. **F. Comino:** Writing – review and editing; conceptualization. **D. Gorvy:** Writing – review and editing; investigation; supervision.

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There was no financial support from any institution for the realisation of the clinical cases.

## CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

## ETHICS STATEMENT

No ethical approval required.

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