Intraluminal administration of a carboxymethyl-starch powder for bladder haemorrhage treatment in two adult horses

Giulia Memoli[1], Lucia Fontana[1], Ilaria Basano[1], Marcello Pallante[1], Andrea Bertuglia[1], and Michela Bullone[1]

[1]University of Turin

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Abstract

Internal bleeding and mucosal bleeding in hollow organs are uncommon conditions in equine medicine and endoscopy. Most of the times, they respond to treatment of the underlying primary condition. However, there are cases in which a rapid and effective control of blood loss is required and the animal is not suited for surgery or general anaesthesia. We report two cases referred to our Veterinary Teaching Hospital with signs of urinary disease and bladder haemorrhage identified by cystoscopy which were successfully managed with topical application of a haemostatic carboxymethyl-starch powder. The product was applied directly on the bleeding mucosa after bladder emptying either under endoscopic guidance or blindly, through a urinary catheter. The application of the haemostatic powder appears to be easy to perform, safe, and helpful in controlling mucosal bleeding in hollow organs in the short time, with no adverse reactions noticed. This approach should be considered in cases where mucosal bleeding can be identified by endoscopy and a prompt control of blood loss is required, also in the field.

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Running title: Bladder haemorrhage treatment

Giulia Memoli, Lucia Fontana, Ilaria Basano, Marcello Pallante, Andrea Bertuglia, Michela Bullone.

Department of Veterinary Sciences, University of Turin, 10095 Grugliasco, Italy.

Correspondence to: Michela Bullone, Department of Veterinary Sciences, University of Turin,

10095 Grugliasco (TO), Italy. Email: michela.bullone@unito.it.

Summary

Internal bleeding and mucosal bleeding in hollow organs are uncommon conditions in equine medicine and endoscopy. Most of the times, they respond to treatment of the underlying primary condition. However, there are cases in which a rapid and effective control of blood loss is required and the animal is not suited for surgery or general anaesthesia. We report two cases referred to our Veterinary Teaching Hospital with signs of urinary disease and bladder haemorrhage identified by cystoscopy which were successfully managed with topical application of a haemostatic carboxymethyl-starch powder. The product was applied directly on the bleeding mucosa after bladder emptying either under endoscopic guidance or blindly, through a urinary catheter. The application of the haemostatic powder appears to be easy to perform, safe, and helpful in controlling mucosal bleeding in hollow organs in the short time, with no adverse reactions noticed. This approach should be considered in cases where mucosal bleeding can be identified by endoscopy and a prompt control of blood loss is required, also in the field.

Keywords: horse, interventional endoscopy, blood loss, bladder, haemostatic powder.

MAIN TEXT

Introduction

Haematuria refers to the presence of red blood cells into the urine, and can be macroscopic or microscopic (Schumacher 2007). Specific data on the incidence of haematuria in equine practice are lacking. However, based on the available evidence, pathologic haematuria is considered uncommon (Duesterdieck-Zellmer 2007; Smith *et al.* 2018). With macroscopic haematuria, urine is red or brown. Discriminating haematuria from pigmenturia (presence of haemoglobin, myoglobin, or pigments in urine) may be challenging and requires laboratory analyses to be performed (Delvescovo 2022). The most common problems associated with haematuria are, in a putative order of frequency: urethral rents, urethritis, urolithiasis, trauma and neoplastic masses, pyelonephritis, cystitis, chronic administration of non-steroidal anti-inflammatory drugs and clotting disorders. Urethral infestation by *Habronema spp.* and *Draschia spp.* larvae, cantharidin toxicosis, renal failure with intravascular haemolysis, and vascular anomalies are other pathological conditions occasionally associated with haematuria (Schumacher 2007). Primary haemorrhagic cystitis is a further idiopathic condition resulting in haematuria. Exercise-related haematuria is also repoted, most often microscopic in nature (Schott *et al.* 1995).

Bladder mucosa has a remarkable regenerative capacity which allows a rapid return to urothelial integrity and function (Saulez *et al.*2005). Bladder haemorrhage often due to cystitis (either infectious, inflammatory, or idiopathic), neoplasia, or trauma. Bacterial cystitis requires mid- to long-term antibiotic treatment and might relapse, depending on the inciting cause. In a previous report on idiopathic haemorrhagic cystitis, most cases resolved completely or almost so in 3 weeks (Smith *et al.* 2018), following prolonged treatment with antimicrobials and anti-inflammatory therapies, despite no bacteria were cultured or identified. These data overall agree with experimental evidence gathered in other species supporting a minimum of 4 weeks for complete healing of damaged bladder mucosa (Hans *et al.* 2019). In spite of the reported positive outcome of prolonged treatment, it is sometimes advisable for the clinician to gain haemorrhage control rapidly, because of the presence of significant anaemia, coagulation disturbances, or because it might also reduce healing time and antimicrobial treatment duration. Urothelium damage can in fact become an entrance port for bacteria into the systemic circulation (Smith*et al.* 2018). On top of this, some horse owners have a strong emotional attitude towards their animal, and will more easily accept therapeutic interventions that control or at least improve the clinical sign(s) for which they looked for veterinary attention in the short-term, joined to other required long-term therapies effective for treating the primary problem.

This report proposes an easy-to-apply topical treatment for rapid bladder bleeding control in two adult geldings diagnosed with haemorrhagic cystitis. The product used is a carboxymethyl-starch powder[a] (CSP) employed in human surgery for blood loss control (Bracey *et al.* 2017). Haemostatic supplements like the one we describe were first used in human medicine in the 40's, and since then their efficacy has constantly improved (Vecchio *et al.*2016). To the best of the Authors' knowledge, this is the first report of trans-endoscopic or trans-catheter application of a haemostatic powder in a hollow organ in equine practice.

Case presentation

We describe the clinical presentation and management of two horses referred to our Veterinary Teaching Hospital (VTH) in 2021 with macroscopic haematuria due do haemorrhagic cystitis, successfully treated with topical CSP. Horse details and case history were recorded in our Institution informatic database[b] and retrospectively reviewed. Animal procedures described in this manuscript have been performed in accordance with the Directive 2010/63/EU of the European Parliament and after acquisition of the owners' Informed Consent.

CASE 1

A 13-year-old Quarter Horse gelding used for American sport disciplines was referred for stranguria of 12 hours' duration, with a suspect of intravesical mass.

At first clinical examination, the horse was bright and responsive, heart rate 36 bpm, respiratory rate 40 bpm,

rectal temperature 37.8°C, normal gut sounds, congested mucous membranes with slightly prolonged capillary refill time (2"). The horse showed constant urine dripping from the penis and appeared to experience pain while walking. The owner reported a sudden increase of muscular masses in the last days. Rectal palpation and ultrasonography revealed distended urinary bladder with mucous and viscous hyperechogenic content, enlarged spleen, and no other abnormalities. Haematology and biochemistry revealed moderate anaemia (hematocrit 26.5%), moderate azotaemia, mild hyponatremia, and markedly elevated levels of creatinine kinase (1.750.000 UI). A diagnosis of myopathy was made, and genetic analysis sent for a panel of breed-associated disorders. They subsequently revealed a heterozygous genotype for MYHM (myosin-heavy chain myopathy) gene and immunosuppressive therapy based on dexamethasone intravenously (IV) at 0,06 mg/kg q24 h for 5 days followed by 1 mg/kg prednisolone PO q24 h, was then instituted. Treatment with aggressive fluid therapy was initiated in association with flunixin meglumine IV 1.1 mg/kg q24 h. The stranguria was ascribed to the unwillingness of the horse to assume urination position due to muscle pain. The bladder was catheterized during the first visit and 7 litres of dark urine with sand deposits were removed. Bladder was washed with sterile saline solution to remove sabulous detritus. Stranguria persisted in the following days of hospitalization, despite analgesic treatment, and blood clots in the urines were observed macroscopically. Ultrasound examination of the bladder revealed a heterogeneous hyperechogenic mass in ventral portion of the urinary bladder (Figure 1D). The ventrocaudal part of the wall appeared thickened (8.4 mm) and oedematous, the rest of the organ presented a normo-echogenic aspect. At cystoscopy, performed using a 160-cm flexible endoscope[c], the bladder mucosa was hyperaemic with diffuse petechiation and deep ulcers appreciable in the ventral aspect of the organ (Figure 1A-B). Macroscopically, urine appeared dark brown to rose in colour, with mucous as well as mucosal fragments and blood clots in suspension. Urine culture was requested (which then yielded a *E. coli* sensitive to trimethoprim-sulfamethoxazole [TMS]) and an initial treatment with 15 mg/kg ampicillin IV q8 h and 25 mg/kg TMS PO q12 h was started. Despite clinical improvements, marked bleeding persisted for up to ten days from the bladder ulcer, with hematocrit gradually decreasing. Local application of CSP on the bladder mucosa where the ulcer was evident was attempted under endoscopic guidance. The CSP (5 g) was gently inserted into a catheter with 1.8mm outer diameter and 190cm length[d], which was then passed through the working channel of the endoscope after bladder emptying. Bleeding from the ulcer was substantial and margins of the lesion were not identifiable for long time. The powder was air pushed through the catheter and immediately created a gel coating over the ulcerated mucosal area. Endoscope was retracted and urine production closely monitored, as we hypothesized that the haemostatic clot could move and generate obstruction to urine outflow. Bladder transrectal ultrasound appearance was also monitored daily in the following days. Frank bleeding stopped in 24 hours after CSP application. The horse did not show pain or stranguria at any time and continue to autonomously void the bladder with the expected frequency. Ultrasonographically, a hyperecogenic halo was evident in the ventral portion of the bladder which gradually decreased in size over the next 7 days, which was interpreted as the clot induced by CSP over the area of ulcerated mucosa, while the mucosa became hypertrophic (Figure 1C-E-F). Treatment with TMS was continued for additional 7 days, when urine cytology and culture were judged negative. A further ultrasonographic control performed 14 days after the end of antimicrobial treatment still identified an area of thickened mucosa (Figure 1G), in the absence of evidence of macro or microhaematuria and inflammation.

CASE 2

A 26-year-old Argentine gelding used for trekking activities was referred to our VTH for anuria of 36 hours' duration and inappetence. Both conditions developed after the horse experienced a severe fall into a ravine during a trek in the Alps. The horse was rescued by a trained team of colleagues that, after sedation and immobilisation, lifted the horse with a specialised tractor equipped with a plank for horse positioning. At initial examination in the field, the horse was administered dexamethasone (0.2 mg/kg) and rehydrated with 5 L of Ringer Lactate IV. The horse was kept under observation at home, two attempts were made for catheterization which did not yield urine voiding. The horse was then referred 36 hours later for the complaints listed above.

Upon arrival at the VTH, the horse was quiet and responsive. Clinical examination revealed mild dehydration

and superficial bruises in the inguinal region, where ropes were applied few days before. A diagnosis of PPID syndrome was suspected based on the observed severe hypertrichosis, but the owner refused testing options. Rectal palpation was normal, the urinary bladder was palpated and appeared full of urine. Palpation did not elicit overt pain response. Ultrasound of the bladder performed at this time was unrewarding. The gelding was thus catheterized and is bladder emptied. Macroscopically, urines appeared dark yellow and concentrated and no further exam was performed. The complete blood cell count showed the presence of mild leucocytosis characterized by absolute neutrophilia and monocytosis. Serum biochemistry revealed hypoproteinaemia, mild hypoglycaemia and hypocalcaemia. Serum triglycerides were also mildly elevated. Haemogas analysis was unremarkable. Fluid therapy was initiated at maintenance rate of 2.5 ml/kg/hour with Ringer Lactate solution together with IV 3% glucose integration. Esomeprazole was also administered IV 0.5 mg/kg q24 hours.

After 12 hours from referral, the patients started urinating normally. Inappetence only partly improved despite normalization of serum triglycerides. Fluid therapy was suspended. On day 4 of hospitalization, the gelding developed haematuria. Urine cytology at this time showed increased red and white blood cells as well as numerous intracellular bacteria (rods). Transrectal ultrasonography of the bladder showed a mild increase in thickness of the urinary bladder wall, particularly in its ventrocaudal portion (0.54 cm, vs. 2.7 mm in the rest of the organ; reference ranges: 0.3-0.6 mm). Cystoscopy revealed a markedly inflamed and haemorrhagic mucosa. Antimicrobial therapy was initiated with TMS PO 30 mg/kg q12 h. Ketoprofen was also administered once IV 2.2 mg/kg. Haematuria did not improve in the following 5 days, while urine leukocyte count did decrease. Inappetence gradually improved. Coagulative profile identified a prolonged prothrombin time. Treatment with topical CSP (5 grams total) was attempted through a 2 m long Foley catheter[e]. Macroscopic haematuria completely resolved in the following 48 hours. The patient was discharged on TMS therapy to be continued for further 7 days (total 14 days of antimicrobial treatment). Urine cytology was performed at the end of antimicrobial treatment and revealed normal parameters.

Discussion

In both cases described, a single local application of CSP improved clinical signs of haematuria in 24 to 48 hours in the absence of any relevant adverse effect. The powder used is a 5-gram biocompatible non-pyrogenic non-toxic second-generation starch product with significant water absorption capacity (64 ml/2 g powder) and with reported complete absorption within 48-72 hours. The product used is available off-the-shelf and does not require further preparations or specific storage. Its mechanism of action is based on the uptake of the water component of the blood, which concentrates blood cells (platelets, serum proteins and blood cells) in a gelled adhesive matrix that accelerates the clotting cascade and also acts as a mechanical barrier that limits further bleeding (Bruckner *et al.*2021). To date, no serious side effects are reported in association with the use of SH powder (migration, foreign body reactions, compression and damage of tissues) (Schmitz and Sodian 2015). Its vegetal nature is thought to decrease the risk of allergic reactions compared to animal matrices (Vecchio *et al.* 2016).

Conclusion

Uncontrolled bleeding of the bladder mucosa may warrant prompt intervention in selected equine cases. In our experience, the topical application of CSP in such cases is supported by its effectiveness at rapidly reducing bleeding and promoting mucosal healing, easiness of application, low cost, and safety profile. This is the first report of trans-endoscopic treatment for bleeding control in equine patients presenting with bladder haemorrhage. Further studies will have to be performed to determine the safety profile of CSP in the equine species, as well as its potential application as an adjunctive therapy in cases of hollow organ bleeding.

Figure legend

Figure 1. Endoscopic and ultrasonography findings of case 1. A-B: Cystoscopy performed when macroscopic haematuria was first noticed. C: Cystoscopy performed 7 days post CSP application, while antimicrobial and anti-inflammatory therapies were on course. Note the protrusion of the mucosa and mild accumulation of sabulous material. E-F-G: Ultrasound images of the bladder respectively at 3, 7, and 21 days post CSP

application (cranial is to the right).

List of Manufacturers' addresses

[a] Starsil Hemostat®, Hemostat Manufacturing GmbH, Velen, Germany.

[b] Provet Cloud, Northhealth, Helsinki, Finland.

[c] PV-SC34L, 10 mm OD, Xion GmbH, Berlin, Germany.

[d] Transtracheal wash catheter, MILA International Inc., Florence, Kentucky, USA.

[e] Alcyon, Cherasco, Italy.

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