Benefits of cyanoacrylate mesh closure following exploratory laparotomy in horses

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Running tittle: Cyanoacrylate mesh closure after colic surgery

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ABSTRACT

Background: Skin closure of laparotomy incisions using topical 2-octyl cyanoacrylate (2-OCA) mesh provides a secure bactericidal barrier in man, which may reduce risk of post-operative incisional complications. The benefits have not been objectively assessed in horses.

Methods: From 2009-2020 three methods of skin closure were used following laparotomy for acute colic including metallic staples (MS), suture (ST) and cyanoacrylate mesh (DP). Closure method was not randomized. Owners were contacted ≥3 months postoperatively to identify complications. For each method of closure, the rate of surgical site infection (SSI) and herniation were recorded, as well as surgical time and treatment costs including those for incisional complications. Chi-square testing and logistic regression modelling was used to assess differences between the groups.

Results: A total of 110 horses were recruited: 17 (15.5%) developed SSI, of which 4/45 (8.9%) in DP group, 9/49 (18.4%) in MS group and 4/16 (25%) in ST group (P=0.23). Twenty-four horses (21.8%) developed incisional hernias: of which 4/45 (8.9%) DP, 17/49 (34.7%) MS and 3/16 (18.8%) ST (P=0.009). Median total overall cost was no different between groups, P = 0.47.

Limitations: A retrospective study with non-randomized choice of closure method.

Conclusions: No difference in rate of SSI or cost was demonstrated, though MS was associated with a higher rate of hernia formation. Despite increased capital cost, 2-OCA proved to be a safe alternative and was no more expensive by the time visits to remove sutures/staples and treat infections were factored in.

INTRODUCTION

Surgical site (SS) complications are frequent after celiotomy surgery in horses, including oedema, suppuration, surgical site infection (SSI), dehiscence and incisional hernia. Rates of SSI published in the veterinary literature vary from 10-37% [1-3] and a host of risk factors have been identified. These include increased bodyweight, increased packed cell volume (PCV), small intestinal resection and post-operative colic signs [6]. As well as increasing patient discomfort and morbidity, SSIs also increase the risk of developing an incisional hernia[4,5], which is why strategies to reduce the incidence have been the focus of a considerable body of research. The closure method of the *linea alba* has been shown to have a significant effect on the rate of such complications[5,7-11,12]. The use of an abdominal bandage has also been shown to be an effective method: likelihood of SSI was reduced by 45% in a group using a bandage during the post-operative period [13]. Incisional trauma and wound contamination occurring during the anesthetic recovery has been proposed as potential causes of SSI development[4], which is why protecting the SS is considered one of the key factors in reducing SSI occurrence. The ideal secure adhesive wound dressing for this role has yet to be identified[14,15].

The cyanoacrylate tissue adhesives are liquid monomers that polymerize in contact with tissue surface in an exothermic reaction creating a strong bridging that bonds the apposed wound edges[17] Developed initially for emergency battlefield use during the Vietnam war, cyanoacrylates adhesives are thought to reduce the risk of SSI in man by eliminating the punctures that result from suturing procedures, avoiding the introduction of skin-borne microorganisms and suture tract infections[16]. Dermabond Prineo® (Ethicon, Johnson & Johnson Medical GmbH, Belgium) is a topical skin adhesive, that combines a self-adhering polyester mesh with 2-octyl cyanoacrylate (2-OCA). This mesh contains an initiator that accelerates the

polymerization of the cyanoacrylate and increases the surface area of contact around the surgical incision. Surgical sites closed with a combination of the polyester mesh and 2-OCA reached a higher holding strength than SS closed with skin staples and subcuticular sutures in an ex vivo study on porcine skin[18]. An added benefit is that 2-OCA is bactericidal against skin microflora[19] and has antimicrobial properties against Gram-positive organisms[20], most likely due to a reaction between the electronegative charge on the cyanoacrylate monomer with the positively charged carbohydrate capsule of Gram-positive organisms[21]. These properties make 2-OCA ideally suited to skin closure after equine colic surgery, where high forces and contamination are difficult to avoid during anesthetic recovery. Only two studies have been published to date, describing the use of the of the glue alone, or the glue and mesh combined after exploratory laparotomy[22,23], and no studies have compared the benefits of the use of 2-OCA glue to other established methods of skin closure.

The aims of this study were first, to show that 2-OCA is safe to apply to the horse's skin. Our hypothesis was that it would be safe to use. Second, to compare rates of post-operative SS complications using 2-OCA with traditional methods of skin closure, such as metallic skin staples and suture. We hypothesized that rates of SS complication of the 2-OCA group would be lower, with implications for reduced morbidity, cost and safety for treating veterinarians.

MATERIALS AND METHODS

Inclusion criteria

Records of all horses that underwent exploratory laparotomy for investigation and treatment of abdominal pain (colic) at a single referral hospital from 2009-2020 were selected retrospectively. Horses that were included survived at least three months after surgery. Horses that underwent a second colic surgery were excluded. The owner of each horse admitted for any procedure, including colic surgery, signed a consent form based on the UK GDPR (General Data Protection Regulation) guidelines.

Surgical method

All horses followed a standardized anesthesia protocol. Pre- and post-operative medical therapy consisted of 1.1 mg/kg i.v flunixin meglumine (Meflosyl®; Zoetis^{TM}) and antimicrobial therapy with 3 days of 15 mg/kg intramuscular (i.m) procaine penicillin (Depocillin®; MSD Animal Health) if no resection/enterotomy was performed; or 5 days of penicillin and 6.6 mg/kg i.v gentamicin (Genta-Equine®; Dechra) if an enterotomy or resection was performed.

For all horses, the *linea alba* was closed in a simple continuous pattern with double strand loop of 5 metric glycolide/lactide copolymer (Polysorb®; Covidien™) anchored with a lark's foot suture and closed with a double throw and at least 5 further throws. The subcutaneous area was closed using a combined continuous subcutaneous suture in 3.5 metric glycolide/lactide copolymer (Polysorb®; Covidien™) to ensure skin apposition. Final dermal apposition differed between the 3 groups and was not randomized: In the 2-OCA group (DP) a self-adhering polyester mesh was applied over the incision, over which the 2-OCA was painted, as shown in Fig 1. In the metallic skin staples group (MS), stainless steel skin staples (Precise^{M} Vista; 3^{M})

were applied at 5 mm intervals. In the sutured group (ST), a continuous Ford interlocking suture pattern using 4 metric monofilament material (Prolene®, Ethicon™)[9] was inserted. Every horse had a protective adherent primary dressing applied to the SS (Primapore®; Smith & Nephew) and covered with a sticky foam-backed adhesive dressing (Animal Polster™; Snogg).

Hospitalization and follow up

An abdominal bandage was applied following anesthetic recovery (CM Equine Products) and changed daily. The primary dressings were removed the following day, to be replaced with a clean Gamgee pad, also changed daily. No dressings were applied after removal of the belly bandage. Surgical site infection was defined as persistent serous or serosanguineous draining starting more than 24 hours after surgery, or purulent drainage, with or without positive bacterial culture[6]. Serous discharge for less than 24 hours after surgery and peri-incisional edema not associated with drainage were not considered signs of SSI[2]. Type of discharge and/or skin reaction and days since surgery to the start of infection were recorded. Incisional hernia was defined as a discontinuity on the apposition of the *linea alba* resulting in a distinct rounded swelling lower than the normal profile of the ventral abdominal wall.

All horses were discharged upon completion of antimicrobials and resolution of the clinical symptoms. Total duration of hospitalization was recorded to the nearest day. All horses were discharged with an abdominal bandage to be worn for an additional three weeks, with the same recommendation to change the bandage and monitor the surgical site daily.

The horses in groups MS and ST had the staples/sutures removed between 10-15 days after the surgery; no routine follow-up visit was requested for the horses in the group DP and owners were advised to simply let the mesh fall off naturally, or with instructions to remove it themselves

from 14 days post-surgery if they wished. If SSI developed, sutures or staples were removed at the time of diagnosis to allow cleaning and drainage. In the DP group, mesh removal was carried out to facilitate drainage. This was accomplished by application of isopropyl alcohol on a cotton gauze swab to soften the mesh before peeling off. Regardless of group, if SSI occurred after hospital discharge, assessment, implant removal and first treatment was always carried out by the primary treating veterinarian.

Owners were contacted by telephone a minimum of 3 months postoperatively to record occurrence of complications, survival and return to use. Primary treating veterinarians were also asked their preference on skin closure method postoperatively, which method they thought was safer and preferred.

Costs

Median cost was calculated for each group and evaluated for comparison using an inflation adjustment to ensure comparable data throughout the study period (consumer prices index, CPI, UK Office of National Statistics, October 2020). The cost of hospitalization consisted of initial work-up, surgery, and postoperative treatment until the date of discharge. Total treatment cost included this plus the additional costs of routine home visits to remove skin sutures or staples, assess hernias and treatment costs for SSI. Costs incurred treating incisional hernias was excluded.

Statistical analysis

It was estimated that 396 horses (198 in each group) would be needed to detect a statistically significant difference at 80% power. Data was collated using a spreadsheet (Microsoft Excel, Microsoft, New Mexico, USA) and statistical tests carried out using MedCalc software

(MedCalc Software Ltd, Belgium). Data was tested for normality using the Kolmogorov-Smirnov test, with significance was set at $p \leq 0.05$ for all subsequent tests. Chi-squared test were used to compare the rate of SSI and hernia formation using the three methods of closure, and these were also assessed for confounding with binary logistic regression models including a term for surgeon. Surgeon was added as a predictor to each univariable logistic regression model and then compared to the univariable model with a likelihood ratio test. Additionally, the impact of inclusion of surgeon on primary risk factor OR was examined. The R Statistical system was used for data analysis (R Core Team 2021).

RESULTS

A total of 171 horses were identified, of which 110 horses met the inclusion criteria. Mean age was 11 years, range 3 months to 28 years. Sixty-nine were geldings, 30 mares, 6 stallions, 4 fillies and one colt. Breeds were: 23 Thoroughbreds/Thoroughbred cross, 15 Warmbloods, 4 Standardbreds, 5 Arabs/Arabs cross, 32 Welsh Cob, 8 ponies, 6 Irish Draught/Irish Draught cross, 5 Sport horses, 2 Connemara, 2 Quarter horse, 1 Lusitano, 1 Friesian cross and 1 dwarf pony. Forty-five horses were in the DP group, 49 MS and 16 ST. Mean surgery time was shorter in the DP group (70 minutes), compared to 85 minutes in the ST and 85 minutes in the MS groups, respectively ($p = 0.02$). The number of DP horses undergoing enterotomy/enterectomy (18/45; 40%) was lower compared to the MS (27/49; 55%) and ST (9/16; 56%) group, which led to longer surgery times in those groups. Mean hospitalization was 6.6, range 3-15 days.

Clinical outcomes

From the total 110 horses, none developed any skin reaction, whilst 17 (15.5%) developed SSI. From the 17 horses that developed SSI, two horses had a culture and sensitivity performed, neither of them had bacterial growth on culture. Among these 17 horses, 4 (8.9%) had skin closure with DP, compared to 9 (18.4%) closed with MS and 4 (25%) with ST. There was no significant difference in rate of SSI (Chi square $P = 0.23$). In the binary logistic regression model with group DP as the reference, neither groups ST (OR 3.24, 95 % CI 0.71 - 16.54, $P = 0.115$) or groups MS (OR 2.31, 95 % CI 0.69 - 9.07, $P = 0.192$) were significantly more likely to develop SSI.

A total of 24 horses (21.8%) developed incisional herniation. Group MS had highest rate of hernia formation, much more so than either of the other two groups (Chi square $P = 0.009$).

Among the 24 horses with hernias, four (8.9%) had skin closure with DP, compared to 17 (34.7%) closed with MS and 3 (18.8%) with ST. In the binary logistic regression model, the risk of incisional hernia with MS was 5.45 times more likely compared to DP (OR 5.45, 95 % CI 1.81-20.37, P = 0.005). Group ST was no different to group DP (OR 2.37, 95 % CI 0.42 - 12.14, P = 0.298). Although limited by small numbers, SSI was not an invariable risk factor for incisional hernia development: One of the 4 horses in group DP with a hernia had a previous SSI, 2 of the 3 in the ST group, and 6 of 17 in the MS group.

Cost & safety

Median hospitalization cost (British pound sterling, GBP) was 3455 for the DP group, 2424 for the ST group and 3228 for the MS group, increased cost reflecting the capital cost of the 2-OCA mesh. Total treatment cost was equivalent between the 3 groups: 3065 (DP), 3020 (MS) and 2844 (ST), P = 0.47. Surveying 18 veterinarians showed that 94% (17/18) felt safer with the use of Prineo due to them not risking their personal safety as they do when they must remove staples or suture. One was concerned that the mesh kept the infection inside, hampering efforts for drainage and cleaning when compared to removing skin staples or sutures.

DISCUSSION

According to our first hypothesis, horses closed with 2-OCA in this study did not experience any reactions after its use, indicating it to be well-tolerated and safe to apply to equine skin after celiotomy. Deep tissue inflammatory response has been previously documented after using *n*-butyl-cyanoacrylate for skin closure[24]. It is possible that the inflammatory reaction in that study was due to the catgut used in the subcutaneous tissues, whereas we used glycolide/lactide copolymer. It may also have been related to the type of glue used. Although from the same chemical family, *n*-butyl-cyanoacrylate is more tissue toxic, brittle and prone to crack[17]. In contrast, 2-OCA is more flexible, and when combined with the mesh provides additional structural reinforcement akin to reinforced concrete.

This study lacked the numbers and hence power to draw conclusions regarding our second hypothesis. Despite this, results from the DP group demonstrated both safety and SS complication rate equivalence compared to traditional methods of skin closure. The theoretical benefits of a strong sealed bactericidal superglue skin closure proved most reassuring when a horse was rolling round the anesthetic recovery suite during recovery. Whether the 2-OCA system tested here is truly the ideal skin closure method espoused by previous studies[14] remains to be shown. Another important limitation to acknowledge was the lack of culture and sensitivity performed in those horses who developed SSI. With the exception of the 2 cases reported, historically this was not routinely carried out. This is because antibiotics have never formed part of the routine management of post-colic surgery SSI for these authors, having been already supplied for the 5 days following laparotomy. Having established open drainage, celiotomy wounds are allowed to heal by second intention with regular saltwater cleaning and occasional application of topical honey. However, the authors now advocate best practice for biosecurity

and antimicrobial stewardship, mandating routine culture and sensitivity testing for monitoring, even if the results do not alter the treatment regime that is carried out. An interesting observation worth of note was the relatively high proportion of horses that developed a hernia without prior SSI. Horses with SSI were reported to be nearly 9 times more likely to develop incisional hernia compared to horses without, 19 % with versus 2 % without[25]. Our results mirrored these findings in the ST and MS groups, but DP was a much smaller proportion. Whether this is a true finding, or more likely simply a random finding, remains to be seen. If true, it suggests that skin closure method and SSI are not the only factors associated with hernia formation.

Having established an equivalent complication rate, the combination of the mesh and the glue maybe be beneficial by reducing the need to remove foreign material from a difficult and dangerous position on the lower abdomen. Because the cyanoacrylate implant effectively removes itself as the hair re-grows, there was no need to have a follow-up visit to remove it. Obviating the need for removal made 2-OCA an attractive solution for celiotomy wounds in horses, reducing costs incurred postoperatively. Some owners did request a remote consultation when they observed the mesh hanging from the hair months later, but with the exception of 4 horses that developed SSI, no veterinarians needed to risk themselves removing anything from the ventral abdomen of these horses. When SSI did occur, removal was still easier than with the other closure techniques, using the isopropyl alcohol technique outlined in materials and methods. This softened the mesh without the need to directly visualize the wound, hence keeping the veterinarian's head further out of kicking range of the hind legs. When SSI did occur, removal was considered important as the mesh tended to trap pus and hinder drainage. A potential criticism related to this was the potential to delay identification and hence treatment of SSI. This could not be objectively assessed either way by this study, but no objective evidence

that the 4 afflicted horses differed in their outcomes was identified, suggesting this to be a theoretical rather than actual problem. Another early practical concern was what would happen if a horse needed a repeat surgery during the first hospitalization period. No horses meeting the inclusion criteria had undergone a second exploratory laparotomy. However, removing the mesh in the same way before returning to the abdomen via the same incision has been successfully undertaken by the authors without issue. Others advocate preserving the original incision and instead, using an alternative ventral paramedian approach to the abdomen for repeat laparotomy[26]. This would be unaffected by the 2-OCA implant, although more recent commercial versions have a slightly wider mesh, pushing the repeat laparotomy further abaxially.

To the author's knowledge no previous studies have objectively compared costs of different closure methods. It is reassuring to see that the significantly increased material cost of the 2-OCA system was not reflected in any detectable difference in overall costs, indicating the safety and security of the system to be cost-neutral. The main limitation of the study is its retrospective clinical nature and the consequent non-randomized choice of closure method, leading to selection bias. Had the closure method been randomised a potentially smaller number of horses might have been needed. Another weakness of retrospective studies like this is lack of availability of potential confounding variables and risk factors, for example incisional length, amount of oedema and pre-operative hematological values, such as hematocrit and lactate. Further randomised prospective studies with larger numbers are clearly warranted.

Overall, the rate of incisional infections (8.9%) and incisional hernia (8.9%) after closure with 2-OCA mesh did not differ from the better reference rates published in the literature after celiotomy, nor from the traditional methods of closure described herein. It proved itself a safe

and effective means of skin closure after colic surgery, with additional safety benefits for veterinarians involved in their postoperative care.

AUTHORS' DECLARATIONS OF INTEREST

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

ETHICAL ANIMAL RESEARCH

In this retrospective study, archived material from patients was used. To use these records, their owners were informed, and written permission was given

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