

Placenta and 5-Fluorouracil Applications in Treatment of Extremity Wounds of Race Horses

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Geliş Tarihi: 15.11.2014 Kabul Tarihi: 19.01.2015

Abstract: This study investigated the effects of placenta and cicatrized pomade applied to the wounds determined at the different sites of the extremities of 5 race horses of ages between 10 months and 6 years, on granulation tissue and epithelial layer. Additionally, the effect of topically applied 5-fluorouracile (5-FU), an anti-proliferative agent on prevention of an exuberant tissue showing development trend in four of the existing cases during healing process was evaluated. At the end of the study, it was observed that placenta accelerated granulation in the wound beds with large tissue loss, 5-FU prevented significantly exuberant granulation and the cicatrized pomade applied to around the wound ensured the continuation of the healing process in a healthy manner, promoting the progress of slowly developing epithelial layer in the extremity wounds.

Keywords: Horse, extremity wounds, treatment, placenta, 5-Fluorouracil

Yarış Atlarının Ekstremitte Yaralarının Sağaltımında Plasenta ve 5-Fluorourasil Uygulamaları

Özet: Çalışmada yaşları 10 ay ile 6 yıl arasında değişen 5 adet yarış atının ekstremitelerinin farklı yerlerinde saptanan maddi kayıplı yaralara uygulanan plasenta ve skatrizan pomadın granülasyon dokusu ve epitelizasyon süreci üzerine olan etkileri araştırılmıştır. Yara iyileşme süreci sırasında mevcut olguların 4'ünde gelişme eğilimi gösteren taşkın granülasyonun önlenmesinde antiproliferatif bir ajan olan 5-Fluorourasil (5-FU)'in topikal olarak uygulanmasının etkileri değerlendirilmiştir. Çalışmanın sonunda plasentanın doku kayıplı yara yatağındaki granülasyonu hızlandırdığı, 5-FU'nun taşkın granülasyonu belirgin şekilde önlediği ve yara dudağına uygulanan skatrizan pomadın ekstremitte yaralarında yavaş gelişen epitel tabakanın ilerlemesini hızlandırarak iyileşme sürecinin sağlıklı şekilde devamını sağladığı gözlemlenmiştir.

Anahtar Kelimeler: At, ekstremitte yarası, sağaltım, plasenta, 5-Fluorourasil

Introduction

Horses are often susceptible to injury because of their habitats, uses and natural instincts (Theoret et al., 2013, Gomez and Hanson 2005). Most equine injuries occur on the distal parts of the extremities. Equine limb wounds have a longer preparatory phase of healing due to greater rate of wound expansion (Dart et al., 2009; Berton, 1989), slower and earlier cessation of wound contraction (Dart et al., 2009; Wilmlink and Van Weeren 2005), slower rate of epithelialization process (Dart et al., 2009; Wilmlink and Van Weeren 2005; Theoret et al., 2001; Berton, 1989; Jaccob et al., 1984), rapid granulation tissue formation (Kılıç and Tosun, 2001; Chvapil et al., 1979) and higher contamination risk (Dart et al., 2009; Wilmlink and van Weeren, 2005; Theoret et al., 2001; Berton, 1989; Jaccob et al., 1984). Granulation tissue formation is faster in horses than all other animals (Kılıç and Tosun, 2001; Chvapil et al., 1979). Rapid granulation tissue formation along with factors such excessive mobility of wound margin and easy contamination decrease further rate of epithelialization and contraction with resultants of delayed healing and exuberant granulation tissue (EGT)

formation or fibroproliferative disorder (Theoret et al., 2013; Kılıç and Tosun, 2001; Howard et al., 1993). Seconder intention healing is usually the method eventually chosen for the treatment of horse limb wounds (Dart et al., 2009; Wilmlink and Van Weeren, 2005; Theoret et al., 2001). To promote second intention healing many types of topical wound healing materials and preparations on the basis of composition, permeability to water vapor, fluids and oxygen and the ability to adhere the wound have been described (Bischofberger et al., 2013; Dart et al., 2009; Gomez and Hanson 2005). In equine distal limb wound studies (Goodrich et al., 2000), during wound healing the placenta was found to promote the epithelialization and contraction processes but to reduce risk of EGT in horses, likely via activities such as hormones, enzymes and growth factors that it contains (Cianfarani et al., 2006; Carmeliet et al., 2001; Alkan, 1987).

Human and horses are the only mammals naturally developing EGT during wound healing (Theoret et al., 2013). EGT formation is attempted

to be controlled by methods such as chemical cautery, cryosurgery and surgical resection.

Surgical resection has an advantage of easy to perform, provides tissue for histological analysis and preserves epithelial front (Barton 1989). Five-fluorouracil (5-FU) is an anti-proliferative drug used to treat different types of cancers and papilloma (Tüzün and Küçüktaş 2010) in human and (Van Den Top et al 2010) in animals.

This agent has been used for the treatment of EGT formation in distal wounds of three horses with promising results. The objective of the present study was to benefit from the accelerative effects of placenta on granulation tissue and cicatrized pomade on epithelialization front and from antiproliferative effect of 5-FU on granulation tissue to treat equine distal wounds faster and with lower rate of complications.

Table 1. Descriptions of the cases, the sites and causes of wounding and times the cases submitted to the treatment (TPST).

Breed	Age	Sex	Wound sites	Wound causes	TCST
English	6 Yrs	F	Mid-caudal aspect of left forearm	Rope entanglement	15 Ds
English	11 Mnts	F	Mid-lateral cannon and dorsal aspect of fetlock joint, left rare limb (Fig 3).	Caught in fence	1 Ds
English	1 Yr	F	Dorsomedial aspect of left rare fetlock joint (Fig 1).	Caught in paddock gate	1 Ds
Arab	1.5 Yrs	M	Lateral, dorsal and medial aspects of knee and dorsal mid cannon of right forelimb (Fig 4).	Caught in fence	2 Ds
English	10 Mnts	M	Mid-lateral cannon of the rare limb (Fig 5).	Caught in fence	0,5 Ds

Materials and Methods

The study consisted of 5 thoroughbred race horses whose details are presented in Table 1. Because of being different degrees of contaminated and infected, all case wounds initially underwent standard wound care (SWC:

debridement, cleansing with antiseptic solution and soft bandage of three-layer dressing, i.e. a nonstick pad against the wound, a protective layer of padding soaked with antiseptic solution and outer wrap (Table 2).

Table 2. Treatment applied, total management time (TMT), follow-up period (FP) and results obtained during the study. FH: Full healing, Ds: Days.

Cases	Treatment stages	TMT	FP	Results
1	RWC ¹ (1x3: 3 Ds) + parenteral antibiotic (1X7: 7 Ds) RWC ² + placenta + bandage (3x10: 30 Ds) RWC ³ + rigid bandage (5X3: 15 Ds)	48 Ds	3 Yrs	FH, minor scar
2	RWC ² + skin suture + parenteral antibiotic (1x7: 7 Ds) Removed macerated skin + RWC ¹ (3x3: 9 Ds). RWC ² + placenta + rigid bandage (3x7: 21 Ds) RWC ² , resection + 5FU + water rinse + cicatrized pomade + rigid bandage (3x8: 24 Ds). RWC ³ +cicatrized pomade + rigid bandage (5X6: 30 Ds)	87 Ds	4 Yrs	FH, scar along healing line (Fig 8)
3	RWC ¹ (2X2: 4 ds) + parenteral antibiotic (1X14: 14 Ds) RWC ² + placenta + rigid bandage (3x7: 21 Ds) RWC ² , resection + 5FU + water rinse + cicatrized pomade + rigid bandage (2X15: 30 Ds). RWC ³ + cicatrized pomade + rigid bandage (5X12: 60 Ds)	115 Ds	2.5 Yrs	FH, scar along healing line (Fig 9)
4	RWC ¹ + parenteral antibiotic (1X14: 7 Ds) RWC ² + placenta + rigid bandage (3x5: 15 Ds) RWC ² , resection + 5FU + water rinse + cicatrized pomade + rigid bandage (5X6: 30 Ds). RWC ³ + cicatrized pomade + rigid bandage (5X6: 30 Ds)	82 Ds	2 Yrs	FH, large scar (Fig 10)
5	RWC ¹ (1x3: 3dys) + parenteral antibiotic (1x10: 10 Ds) RWC ² + skin suture (1x14: 14 Ds) RWC ¹ (2x5: 10 Ds) RWC ² , resection + 5FU+ water rinse + cicatrized pomade + rigid bandage (2x5: 10 Ds). RWC ³ + cicatrized pomade + rigid bandage (5x9: 45 Ds)	92 Ds	0.7 Yrs	FH, local scar (Fig 11)

Routine wound care (RWC¹): debridement, cleansing with antiseptic solution and wet bandage. RWC²: debridement if required and cleansing with antiseptic solution. RWC³: debridement if required and cleansing with soap and warm water.

After SWC, the wounds of three cases were closed with simple interrupted or horizontal mattress sutures that were totally dissolved short after the application. Thus, the wounds of these three cases underwent once again to open SWC procedures. In all cases antiseptic cleansing was replaced with just soap and water once sign of infection and local swelling subdued. This process was repeated in every bandage change until a completed healing for a particular case was obtained (Table 2). The placenta procured and prepared according to criteria described before (Kılıç et al., 2002) was applied (Figure 1) to the wound of four cases with large granulation tissue losses (Figure 2-4) in a duration of 15 to 30 days depending on requirement (Table 2). Application was ceased when wound beds was completely filled with granulation tissue. During healing

process EGT (Figures 3-5) developed in four cases. In these cases following EGT resection, wound surface hemostasis was provided with compression utilizing gauze and cotton pad. After the wound surface let air-dried 5-FU soaked gauze pad was applied topically fixing in place with plaster (Figure 6) for an hour. This application was repeated 2-6 times during 10-30 days depending on case requirement. During this administration epithelialization front was protected with a nylon sheet containing a hole corresponding to the size of the granulation tissue area (Figure 7). After removing the temporary bandage, the wound surface was thoroughly rinsed with warm tap water, the wound surface was air-dried, cicatrized pomade was applied to around the wound margin including epithelialization front with massage and then rigid bandage was applied.



Case 3: Placenta is applied (Figure 2), the wound with large tissue loss, first phalanx is exposed (Figure 1). Cases 2, 4, 5: Appearance of EGT (Figure 3-5). Case 5: 5-FU soaked pad fixed in place temporarily (Figure 6), wound surface was limited to a nylon layer contained a hole corresponding to its size and fixed in place with plaster and surgical section is performed (Figure 7). Cases 2-5: the wound healed with different degrees of scars (Figures 8-11).

Results

A full recovery was achieved with open wound treatment and placenta application after the wound of the first case closed initially with sutures resulted in failure due to skin necrosis and infection. The sutures applied to the second case were also opened for the same reasons. An open wound treatment was started with placenta application. Upon entry of the wound into EGT tendency the placenta application was terminated. EGT was prevented by surgical resection and administration of 5-FU. With the help of epithelialized ointment applied to the wound margin a full recovery the exception for a cicatrix trace in

the wound site was achieved (Figure 8). It was determined that in the third case having large and deep injury the granulation tissue loss (Figure 2) was quickly recovered with placenta application after wound asepsis was provided. EGT developing the healing process was inhibited with surgical resection and topical 5-FU administration. Through the treatment protocol including cicatrized ointment it was observed that the wound completely covered by the epithelial tissue in a total of 115 days and a complete recovery ensured during 2.5-year follow-up period (Figure 9). To the third case characterized with large thorn wound in

lateral, dorsal and medial aspects of knee and dorsal mid cannon of right forelimb (Figure 4), placenta application was tried for 15 days after assessing to have no benefit of the suturing due to the mobility of the region and ensuring the asepsis of the wound. As before EGT was solved with surgical resection and topical 5-FU application. With stimulation of an epitheliotropic ointment applied a full recovery ensured in 82 days (Figure 10). In the last case because the wound had recently occurred the sutures were applied after SWC procedure. However, they began to open about 5 days later due to developed subcutaneous infection. At that time partial skin regression occurred due to the adhesion developing between the skin and underlying the tissues. Surgical resection and topical 5-FU application applied several time to eliminate EGT developed (Figure 5). With an aid of the ointment applied the healing was provided in 92 days (Figure 11). At the end of the treatment protocols all case wounds healed with duration of 48 to 115 days with different degrees of scar traces in the wound sites (Figures 8-11).

Discussion

In horses as were in the present cases the wounds with extensive tissue loss commonly occur and of which few are amenable to primary closure (Dart et al., 2009; Wilmink and Van Weeren, 2005; Theoret et al., 2001). Second intention repair occurring with formation of granulation tissue is subjected to a number of complications leading frequently to such as ulcerative lesions and those in distal limbs to EGT which can cause lameness (Theoret et al., 2013). Primary and second intention wound repairs of the distal limbs of horses are often hampered because of swelling from chronic inflammation and excessive mobility of the wound site (Gomez and Hanson, 2005). The cases used in the present study underwent different treatment managements ranged from 48 to 118 days. Alford et al. (2012) similar to present and other authors (Caston, 2012) mentioned that distal limb wounds occur commonly in horses and that its treatment can be frustrating for owners and veterinarians and managing such wounds as understood from our results is often very expensive, labor intensive and prolonged.

The cutaneous healing process is hampered by complications like excessive scarring, detrimental to functional and esthetic outcomes (Theoret et al., 2013). During the present study, wound healing process led to EGT formation in 4 horses. This abnormality was judged as an obstacle to epithelialization front expanding over the

wound surface to complete the healing process. As there is no magic ointment, salve or injection that can make wound healing easy cases specific alternative treatment protocol should be applied (Caston, 2012). Referring current broad treatment spectrum, decisions on wound management should be based costs and the symptom management properties (Dumville et al., 2011). With a proper and effective treatment approach a successful wound healing process can be established (Alford et al 2012). Hence, in this study, on the one hand EGT was tried to be prevented combining the beneficiary characteristics of rigid bandage, surgical excision, antiproliferative action of 5-FU on granulation tissue, on the other hand excessive granulation tissue loss and epithelialization process was promoted applying placenta and cicatrized pomades. In horses used in the study depending on factors such as wound sizes, oldness and localizations, the wound surfaces were covered with epithelialization layer in the time periods mentioned above, however, provision of a full healing along with gaining normal function of the animals were determined to be established even in a more prolonged period. At the end of this process in all animals no functional abnormality apart from some minor cosmetic concerns like scars remained. Thus, it is understood from management and follow-up period of the present that prolonged healing process is followed by years of remodeling processes (Theoret et al., 2013; Alford et al., 2012).

The effects of semi-occlusive and occlusive dressings, artificial skins, collagen and amniotic membranes, biosynthetic dressings, vitamins, and nutrients on healing processes of equine extremity wounds have been evaluated (Kelleher et al., 2014; Kılıç and Tosun, 2001). In management of the wounds left healing with second intention, dressing materials with lower risks of trauma and contamination and higher characteristics of absorbing excess exudate and stimulating the repair are often suggested (Gomez and Hanson, 2005). In the present study, various magnitudes and deepness of the wounds determined in different locations of the extremities of 5 thoroughbred horses aged between 10 months and 6 years were freed from infection undergoing primarily debridement, mechanical cleansing, irrigation and antiseptic wet bandage (Caron, 1992) and prepared for necessary surgical intervention. After this preliminary attempt the wounds in three cases thought to be suitable were closed with sutures. In two of these cases, surgical intervention resulted in failure due to developed skin necrosis because of local circulation impairment, sutures ruptures due to excessive skin

tension with swelling and infection developed because of the clients' negligence (Gomez and Hanson, 2005). In the third case that sutures were applied, even though all sutures opened with similar reasons as above, due to pre-developed adhesion with the wound bed the skin partially retreated leaving in place relatively a smaller size of wound surface compared to its preliminary form. Therefore, compared to other two had sutures, in this case, it was managed to obtain a wound healing with advantages such as minimum time loss, lower cost and minimum scar. In two of 5 cases as large skin losses provided no possibility for primary intention healing in the light of a previous study (Gomez and Hanson, 2005) it were decided directly to apply routine open wound treatment procedures. In total of 4 cases, one the present and 3 others, RWC was also strengthened with a full occlusive organic dressing, the placenta. After cleansing all dirt and necrotic tissues of and freeing microbial contamination from the wounds this organic layer was applied a duration ranging from 15 to 30 depending on their sizes and subcutaneous tissue losses. Placenta is characterized with promoting granulation tissue formation via hormonal and enzymatic properties and growth and vasoactive factors it contains (Cianfarani et al., 2006; Carmeliet et al., 2001, Alkan, 1987). Granulation tissue should be encouraged especially in early phase of wound healing due to its active role on wound contraction process and resistance to infection especially in acute phase of injury (Caron, 1992). In the present study, placenta application was observed to promote a healthier granulation tissue reduce predisposition to EGT compared to spontaneous formation (Kılıç and Tosun, 2001). Because equine distal extremity wounds are well known to prone to EGT (Theoret et al., 2013), the application of placenta was ceased just before healthier granulation tissue loss be evolved to the stage of EGT. Placenta may promote EGT when it is used in wounds with no granulation tissue loss and those tissue loss compensated. A study comparing the effect of equine amnion with a gauze pad has determined that wounds dressed with a gauze were required more frequent EGT excision but longer healing period (Dart et al., 2009).

Bandage is reported to effect wound management positively in early whereas negatively in delayed forms of wounds (Berone, 1989; Kılıç and Tosun, 2001; Goodrich et al., 2000). In the current cases the wounded legs were kept under rigid bandage throughout the treatment period, during which as no complication related to bandaging was encountered after all a full healing has also been achieved. Considering prolonged

treatment period, bandage may be thought somewhat to have delayed the healing process (Berone, 1989; Goodrich et al., 2000). However it may have done a positive contribution to the healing process to proceed in healthy way reducing risks of contamination, infections and myiasis that are quite difficult to prevent in equine distal extremity open wounds (Kılıç and Tosun, 2001; Goodrich et al., 2000; Berone 1989). Excessive mobility of the wound edge may play an important role on formation of EGT assumed as one of the most frequently met complications in equine distal extremity wounds (Caston, 2012). It is also supposed that rigid bandage may minimize the degree and frequency of EGT via providing the wound edge stability (Berone, 1989).

5-FU, an antiproliferative agent, is used as a purpose for chemotherapeutic to treat many malignant tumors parantly (Tüzün and Küçüktaş, 2010) and for regression of wart and corns topically (Van Den Top et al., 2010). Benefiting from its antiproliferative action, 5-FU was used in order to prevent or slow down excessive reformation of granulation tissue after excision of EGT detected in our 4 cases. In parallel to the result of our former case report (Kılıç and Tosun, 2001), 5-FU was seen to successfully lead the recovery in wounds in all present cases, facilitating the progress of the epithelialization over the wound via slowing down excessive granulation tissue formations and causing regression of EGT. The expected effect of 5-FU depends on the topical application be limited to granulation tissue but the epithelial layer not to be affected from the application. Epithelial layer is preserved with a windowed nylon film placed over the wound. Thus, it was concluded that 5-FU can be used safely and would be an alternative treatment option in the wound types mentioned. However, for disclosing fully the positive or negative side of the agent it is required to perform a comparative study using histopathological data along with clinical findings in experimentally created wounds in the distal extremity of horses prone to EGT.

The factors such as genetic predisposition, size, excessive mobility of the wound margin, infection and mechanical irritations (Dart et al., 2009; Kılıç and Tosun, 2001) are well-known causes of equine EGT development. From this event, it is thought that a mismatch caused by the slow development of epithelialization process in the skin and rapid growth in the granulation tissue play an effective role. This contrast process has been effective to establish current therapeutic profile. The exceed granulation tissue over the wound bed is an obstacle to growth of epithelial layer that

normally progresses parallel over the surface of the wound. Therefore, the granulation tissue tended to overgrowth, was tried to eliminate with excision and 5-FU application. That way stopping the overgrowth of granulation tissue is a temporary solution. The important thing is that this tissue needs to be close by the outer epithelial layer. This can be possible if epithelialization front propagate fast over the wound surface and confines the granulation tissue underneath. The proliferation process of epithelialization front was tried to promote applying cicatrized ointment by a massage around the wound margin simultaneously with 5-FU.

The development of EGT has been tried to be suppressed using alternative managements, such as exposing the wound surface to air, keeping the wound under dry bandage, bandaging the wound after applying silver-sulfadiazine like topical antimicrobial agents (Berry and Sullins, 2003), cortisone pomades and collagen gels (Berton 1989) with friction, or covering it with povidone-iodine like antimicrobial impregnated gauze pad, antimicrobial agents in slow release matrix (Berry and Sullins, 2003), with organic occlusive dressing like amnion or platelet rich plasma (Monteiro et al., 2009). The chemical cautery, cryosurgery, and surgical resection are of the types of managements usually used to neutralize the EGT developed (Kılıç and Tosun, 2001; Barton 1989). Surgical resection has an advantage of easy to perform, provides tissue for histological analysis and preserves epithelial front (Barton, 1989). In the present study EGT was determined in four out of 5 cases. This incidence was treated with rigid bandage after surgical resection in a case. In other three cases following surgical resection and prior to bandage, 5-FU was applied topically 2-6 times during a period of 5-30 days depending on the sizes of wound surfaces and frequency in reoccurrence. From this application it was aimed at the prevention of exuberant granulation development via suppressing granulation tissue benefiting from antiproliferative characteristics of the agent. Thus, common cell and intercellular ground substance destruction observed during chemical cauterization have been hindered and its undesirable effects on the healing process (Barton, 1989) have been prevented. Cortisone is mentioned to be used for the prevention of GTF and being more effective in the wound exposed directly to air (Barton, 1989). Because of its potent immunosuppressive agent 5-FU can be more effective on EGT than cortisone and therefore it should be preferred to cortisone in cases highly predisposal to ETF.

In the treatment of horse distal extremity wounds, the effect of platelet-rich plasma application on promoting healthy wound healing and slowing granulation tissue was evaluated considering the rate of contraction in the wound surface, the number of EGT be excised and growth factor type I and III collagen mRNA ratios in excised EGT tissue until a full recovery provided (Monteiro et al., 2009). It was concluded (Monteiro et al., 2009) that topical platelet-rich plasma application had no effect on accelerating or improving the quality of repair of distal limb wounds of horses and that this treatment may better suit wounds with massive tissue loss or, alternatively, chronic wounds that would require a fresh source of mediators to accelerate the healing process. In the present study, placenta instead of platelet-rich plasma was applied to the horse wounds with similar characteristics in order to promote healing process and improve the quality of healing. In wounds with large tissue loss, after obtaining an aseptic environment and completion of granulation tissue formation, healing is provided with skin grafts and in such cases free skin grafts are preferred (Ramsey et al., 1995; Howard et al., 1993). In this study, considering economic reasons, preference of animal's owner and risk of rejection of the free skin graft and risk of anesthesia and cooperative behavior of animals, the healing processes was continued with combination of excessive tissue excision, topical application of 5-FU and rigid bandage. As a result, in cases underwent this treatment full recovery apart from minor cosmetic concerns with regard to scars in wound places was obtained.

In conclusion, it was observed that placenta accelerated granulation in the wound beds with large tissue loss, 5-FU prevented significantly exuberant granulation, the cicatrized pomade applied to around the wound ensured the continuation of the healing process in a healthy manner, promoting the progress of slowly developing epithelial layer in the extremity wounds.

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