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Case Report
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Supplementation of equine placenta extract on corneal wound in two dogs: Case report

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Abstract

Background: Canine corneal disease is a common condition encountered in daily practice. If the depth of corneal damage is limited to the epithelial layer, healing is often straightforward; however, if it extends into the epithelial basement membrane or corneal parenchyma, surgical treatment is the treatment of choice. Moreover, in cases where there is an underlying disease or where the owner refuses surgical treatment, treatment options are often limited to eye drop treatment, which may be inadequate.

Case Description: Dogs aged 10 and 14 years were admitted to the hospital with eye injuries. Based on the examination findings, the owner believed that surgical treatment would be effective; however, this could not be performed owing to the underlying condition of the cases. Hyaluronic acid and antibiotic eye drops were administered, but there was no improvement in the eye damage. The eye-drop treatment was prolonged without any improvement, and in the meantime the patients' weakness became apparent. In parallel with the eye-drop treatment, the patients were given a supplement containing equine placental extract to help restore their physical fitness. Consequently, in addition to the recovery of physical fitness, a film gradually formed over the eye damage area and injuries improved eventually.

Conclusion: Based on these cases, supplementation with equine placenta extract may be an effective treatment option for ocular conditions that are difficult to treat surgically.

Keywords: Corneal wound, Dogs, Placental extract, Supplementation.

Introduction

Corneal epithelial cells in the superficial layer of the cornea form a protective barrier against harmful substances. Growth factor-mediated corneal epithelial regeneration plays a functional role in maintaining barrier function and corneal transparency (Li and Lu, 2005). Corneal injuries resulting from trauma, disease, or surgery are common ocular causes of canine disease seen by veterinarians in both general and specialist practices worldwide.

The causes can be endogenous, including physical, chemical, and nutritional disorders. While corneal injuries often heal easily when the depth of damage is limited to the epithelial layer, a severe transition occurs when the epithelial basement membrane or corneal parenchyma is involved. In such cases, surgical treatment is the treatment of choice, when conservative treatment is ineffective or the deeper parenchymal layer is absent. However, the regenerative capacity of corneal cells after damage or surgery is limited and transplantation of functional donor corneas may be required (Hoppenreijs *et al*., 1994). Potential corneal regeneration is a complex process involving expansion, migration, fusion, and mitosis (Waring *et al*., 1982).

Placental extracts are obtained via enzymatic digestion of the placenta. Human placental extract has been prescribed for the treatment of chronic hepatitis, cirrhosis, and other liver diseases for nearly 50 years. However, the use of human placental extract is restricted in Japan and other countries; therefore, porcine and equine placental extracts (eqPEs) have been developed as alternatives and have been used as ingredients in health foods. eqPE was developed as a supplement for companion animals and has been found to improve liver function and restore physical strength in sick dogs. Moreover, cases have been reported of improvement in symptoms in dogs suffering from protein-losing enteropathy and severe anemia (Fukushima *et al*., 2022; Kotoku *et al*., 2023).

While obtaining more cases of recovery of physical strength by the administration of eqPE, we noted a case of a dog with corneal damage that was difficult to

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treat surgically owing to underlying diseases of liver, kidney, and heart dysfunction and frequent cyanosis. Although this case was treated with eye drops, the corneal damage did not improve. Treatment with eye drops was prolonged and the patient eventually became debilitated owing to worsening of the underlying disease. Therefore, we administered eqPE to restore the patient's physical strength and found that the corneal damage improved. In addition, we encountered another case with similar conditions and when we performed the same treatment, a similar improvement in corneal damage was observed. These cases are discussed in this case report.

Case Details

Case 1

A 10-year-old female Welsh Corgi (18 kg, spayed) was presented to the clinic with an eye abnormality due to trauma. A clinical examination, in addition to an interview to confirm clinical symptoms and a fluorescein stain, was performed, but a definitive diagnosis was not reached. Therefore, the diagnosis was "suspected deep corneal ulcer" (Fig. 1, left). The patient had liver, kidney, and heart disease, as well as a decreased appetite, weakness, and frequent cyanosis. Based on these findings, the owner was informed that surgery requiring anesthesia was risky. Consequently, the owner refused surgery and opted for eye drop therapy. Therefore, we initiated treatment with eye drops. Although purified sodium hyaluronate (hyalurane mini eye drops 0.3%, 3–5 times daily), ofloxacin (ofloxacin eye drops, *ter in die* [tid], daily), and planoprofen (nifran eye drops, tid, daily) were administered for approximately 5 months, no improvement was observed in the eye damage. In the case of severe hyperemia, the antibiotics were temporarily stopped and resumed when the hyperemia had reduced to some extent. Amoxicillin hydrate (Pasetocin tablets, *bis in die* [bid], daily) was administered additionally for a month; however, no change was observed in the eye damage. Moreover, it was observed that the patient's physical fitness had significantly deteriorated owing to a reduced quality of life. As previous clinical experience had empirically shown that eqPE was effective in restoring fitness, eqPE (2 ml, *semel in die* [sid], daily) was initiated to restore physical fitness. The administration of the aforementioned eye drops was continued after eqPE therapy. Twenty-four days after eqPE administration, capsule formation was observed at the ocular damage site (Fig. 1, right panel). No worsening of corneal symptoms or adverse events were observed during the period of eqPE administration. Approximately 1.5 years have passed since the improvement in corneal damage was observed, and no worsening or recurrence of corneal damage has been observed at follow-up visits.

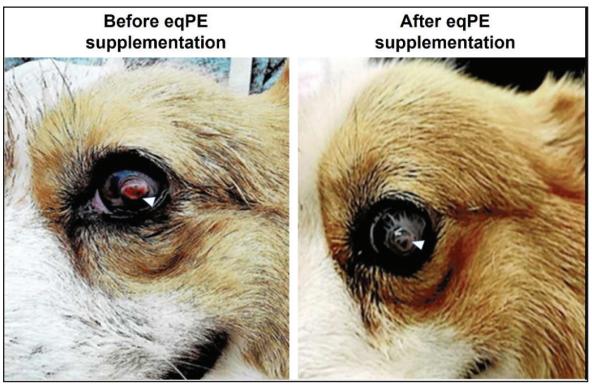

Fig. 1. Appearance of the corneal damage before and after eqPE supplementation (case 1). Before eqPE supplementation (left) and 24 days after eqPE supplementation (right). The triangles indicate ulcerated areas.

Case 2

A 14-year-10-month-old female poodle (3.34 kg, spayed) was presented to our hospital because of frequent eye-rubbing gestures and excessive eye discharge persisting for several days. Although clinical symptoms, visual examination, interview, and fluorescein staining were performed, a definitive diagnosis could not be made. Therefore, a diagnosis of "suspected corneal ulcer" was made based on the findings. As the owner did not want surgical treatment owing to the advanced age of the patient, ophthalmic treatment was administered. The administration of 0.3% HA mini-eye drops (sodium hyaluronate, 3–5 times daily) and mixed eye drops (ofloxacin 2.5 ml/ planoprofen 2.5 ml, 3–5 times daily) was initiated. Levothyroxine sodium hydrate (thyrazine, 100 mg, *bis in die* [bid], daily) and ocracitinib maleate (apokil tablets, 3.6 mg, bid, daily) were also administered as the patient had hypothyroidism and atopic dermatitis. Although rupture of the anterior cruciate ligament and patellar luxation were observed in the right hindlimb, no treatment was administered at the owner's request. Hyperemia and excessive eye discharge subsided 6 days after initiating treatment; however, no improvement in the corneal defect was observed (Fig. 2, Day-6 and Day 0). Considering the treatment of the ocular damage in this case, information regarding case 1 was obtained through personal contacts. This case had similarities to case 1 in that the dog was older, had ocular damage, had other medical conditions and the owner refused surgical treatment. Therefore, administration of eqPE was considered a potential breakthrough, and treatment was administered. Based on the findings of case 1, the administration of eqPE (2 ml, sid, daily) was initiated in combination with the administration of ophthalmic eye drops. An improvement in the corneal damage was observed after 1 week of eqPE administration (Fig. 2, Day 7). No changes were observed in the scores for hyperemia (vasodilation) and eye discharge; however,

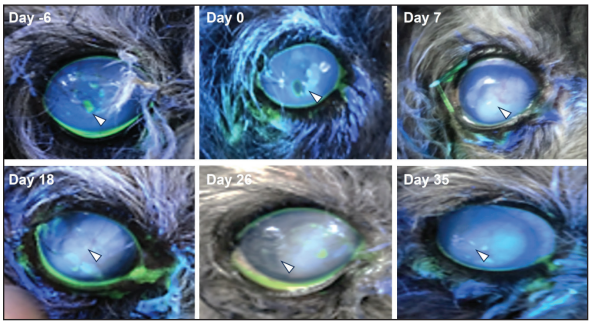

Fig. 2. Changes in the appearance of the corneal damage before, during interruption, and after resumption of eqPE supplementation in case 2. Day-6: before eqPE supplementation, Day 0: start of eqPE supplementation, Day 7: 7 days after initiating eqPE supplementation, Day 18: Interruption of eqPE supplementation, Day 26: Day 1 of resumption of eqPE supplementation, Day 35: Day 10 after the resumption of eqPE supplementation. The triangles indicate damaged areas.

the scores for keratitis (clouding of the cornea), degree of the corneal wound, and angiogenesis decreased from 2 to 0 (Fig. 3, upper panel). The administration of eqPE was continued until day 14, but it was discovered that the owner did not have sufficient amounts of eqPE in stock to continue administration after day 15. Thus, the administration of eqPE supplementation was not performed until day 18. On examination, worsening of the corneal damage was observed on day 18 (Fig. 2, day 18). Moreover, the scores for hyperemia (vasodilation), keratitis/clouding of the cornea, degree of corneal wound, angiogenesis, and eye discharge increased to 2, 2, 4, 4, and 3, respectively, compared with those on day 7 (Fig. 3, upper panel). The administration of eqPE was resumed on day 25, 12 days after day 15, when eqPE was not available (Fig. 3, lower panel). An improvement in the corneal ulcer symptoms was noted on day 26 (Fig. 2, day 26). Although there was no change in the scores for hyperemia (vasodilation), the scores for keratitis/clouding of the cornea, degree of corneal wound, angiogenesis, and eye discharge decreased to 1, 1, 1, and 2, respectively, compared with those on day 18 (Fig. 3, lower panel). The administration of eqPE was continued subsequently (Fig. 3, lower panel), and an improvement in the corneal damage was observed on day 35 (Fig. 2, day 35). In addition, the scores for hyperemia (vasodilation), keratitis/clouding of the cornea, degree of corneal wound, angiogenesis, and eye discharge decreased to 0 on day 35 (Fig. 3, upper panel). The owner was satisfied with the treatment outcome as an improvement in the corneal damage was observed, and the treatment was terminated at the owner's request. Approximately 1 year has passed since the end of treatment, and recurrence of corneal damage has not been reported.

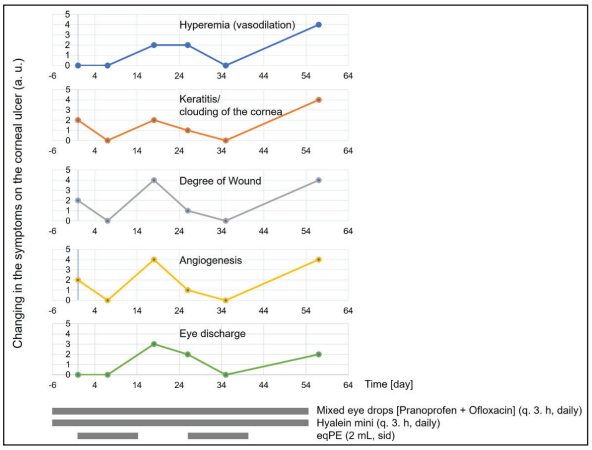

Fig. 3. Subjective assessment of corneal damage before, during interruption, and after resumption of eqPE supplementation in case 2. Upper panel: Subjective evaluation scores after eqPE supplementation. Higher values indicate worsening of symptoms, whereas lower values indicate improvement in symptoms. Lower panel: duration of use of eye drops and eqPE as per standard treatment. The duration of use follows the time axis of the upper diagram.

Ethical approval

No ethical approval was required for these cases.

Discussion

The addition of eqPE supplementation to standard therapy improved the symptoms of corneal damage in both cases. Although the purpose of administering eqPE in these cases was only to restore fitness, it also resulted in an improvement of the diseased ocular area. To the best of our knowledge, no study has reported an improvement in corneal damage following the administration of supplements, especially placental extract supplements, in combination with standard treatment. Therefore, this case report is novel in that an improvement in the symptoms of a patient with inoperable refractory corneal damage was achieved by supplementing conventional standard therapy with placental extract without the requirement for additional standard therapy or drug modification. Thus, this method may be considered in similar cases.

In Case 1, the findings suggested that surgical treatment with a third eyelid flap would be effective. However, owing to the physiological problems associated with the underlying disease in this case, surgical treatment requiring anesthesia was high risk. In fact, the owner refused surgical treatment because of the high risk. Thus, eye-drop therapy was the only viable option. However, eye-drop therapy was unsuccessful, resulting in intractable corneal damage and declining physical health. Therefore, we first attempted to maintain the fitness of the patients by implementing other treatment methods. In case 1, placental extract was initiated because of clinical experience with two large dogs with

unexplained immobility in the past, in which placental extract was administered, with the owner's consent, to restore their fitness, resulting in an improvement in their immobility. The eqPE mainly comprises bioactive peptides, amino acids, minerals, nucleobases, and other nutrients; thus, it was speculated that the placental extract may aid in nutritional supplementation. However, it is unclear whether the results achieved in this study can be attributed solely to the nutritional role of the placental extract. Placental extracts contain bioactive peptides (Yagi *et al*., 1998; Togashi *et al*., 2002; Tohda *et al*., 2021). A representative example is JBP485, which promoted wound healing in the corneal epithelium and the secretion of tear fluid and mucin in the ocular surface epithelium in animal models (Nagata *et al*., 2015; Nakamura *et al*., 2015). In light of these findings, it was hypothesized that the bioactive peptides present in the placental extract also contributed to the improvement of the symptoms in this case.

Case 2 showed improvement in approximately 1 month, unlike case 1, wherein an improvement in the symptoms was observed approximately 7 months after initiating treatment. Rapid sharing of the medical information of case 1 contributed greatly to this improvement and prevented the incidence of refractory symptoms. Worsening of symptoms, presumably due to the discontinuation of placental extract supplementation for various reasons, was observed. Although the literature review did not reveal any cases of canine corneal damage caused by interruption of supplementation, a similar case was reported in human medicine. A similar phenomenon was observed in a patient receiving plasmacytoid supplementation, wherein plasmacytoid dendritic cell activity remained high during the period of plasmacytoid intake but declined slowly when the intake was interrupted (Suzuki *et al*., 2015). Although limited by the inter-species differences and differences between healthy and diseased individuals, these findings suggest that placental extracts must be administered continuously. However, the administration of some supplements is associated with the risk of adverse events, often due to inappropriate dosage or frequency of intake; discontinuation of the intake of the supplements is recommended in such cases (Ronis *et al*., 2018). No adverse events due to the administration of placental extract were observed in our cases, and the interruption of the administration of placental extract was due to the lack of inventory control. No scientific evidence is available to determine the appropriate dosage for placental extract supplementation. However, veterinarians have empirically and experimentally established approximate dosages and guidelines with the consent of pet owners. For dogs weighing less than 10 kg, 2 ml of placental extract must be administered once daily, whereas for dogs weighing more than 10 kg, 4 ml of placental extract must be administered once daily. No adverse events, with the exception of diarrhoea and soft stools, were observed in the several hundred cases receiving placental extract between 2012 and 2023. We previously reported a case of remission of protein-losing enteropathy after 1 year of continuous administration of placental extract and an improvement in suspected immune-mediated haemolytic anemia after 2 years of placental extract administration (Fukushima *et al*., 2022; Kotoku *et al*., 2023). However, as each of these results is a case report of a single patient, there are limitations to the inferences drawn regarding the incidence of adverse events owing to the administration of placental extract. The resumption of placental extract administration after the worsening of symptoms due to the interruption of supplementation resulted in an improvement in symptoms. Thus, it is unlikely that the placental extract had any adverse effects, and its administration is considered to have contributed to the improvement observed in this patient.

Oxidative stress in the form of increased malondialdehyde (MDA) levels and decreased total antioxidant capacity (TAC) and catalase (CAT) levels in tear fluid has been observed in canine and feline corneal ulcers (Farghali *et al*., 2021). The increase in the MDA levels was speculated to be due to increased reactive oxygen species output or decreased antioxidant levels (Salem *et al*., 2020). In addition, changes in corneal hydration have been reported to result in oxidative stress (Kubota *et al*., 2011), which plays an important role in corneal ulceration. Healing of refractory corneal damage after adjuvant therapy with coenzyme Q10 eye drops, an antioxidant, has been reported (Gumus, 2017). One of the best-known effects of placental extracts is their antioxidant effects, for which several molecules have been identified (Togashi *et al*., 2000; Watanabe *et al*., 2002; Togashi *et al*., 2002). Furthermore, placental extracts have been shown to activate Nrf2, a master regulator of phase II enzymes, and promote the expression of heme oxygenase 1, NAD(P)H, quinone dehydrogenase 1, CAT, and superoxide dismutase 1 (Yamauchi *et al*., 2020). This suggests that the antioxidant properties of the placental extract contributed to the improvement of ocular damage in both cases.

Placental extract supplementation was used in combination with standard therapy in the two cases presented here, and it is unclear whether the administration of placental extract alone is effective in treating canine corneal damage. However, as an improvement in symptoms was observed after the administration of the placental extract, the possibility that the placental extract itself had a therapeutic effect cannot be excluded. To the best of our knowledge, there have been no reports on the contribution of placental extracts to the improvement of corneal damage. Moreover, since placental extract has antioxidant and wound-healing effects (Togashi *et al*., 2000; Watanabe *et al*., 2002), it may have contributed to the combined improvement in the two cases. However, a clinical

study with a control group is required to test this hypothesis.

Both dogs in this study were older. Therefore, the effect of administering placental extract in younger dogs is unclear. In cases of corneal ulceration without serious underlying diseases, it is assumed that the administration of placental extract is unlikely to be necessary as surgical treatment is often possible in young dogs. However, if surgical treatment is not possible for various reasons, such as the owner's unwillingness to pursue surgical treatment or inability to administer anesthesia owing to a serious underlying disease, placental extract supplementation is likely to be highly effective.

Although the relationship between corneal ulcers and age in dogs is unknown, aging is a major cause of disability, disease, and death in adult dogs. One of the main consequences of aging is a decline in physical function, which increases the susceptibility to various diseases (McKenzie and Chen, 2022). Case 1 had impaired hepatic, renal, and cardiac functions, whereas case 2 had hypothyroidism, atopic dermatitis, rupture of the anterior cruciate ligament, and patellar luxation in the right hindlimb, and cerumen adenoma. The influence of placental extract supplementation on these hypofunctions in case 1 is unknown, as no aggressive treatment was administered for these hypofunctions in view of the patient's advanced age (14 years). In case 2, placental extract supplementation did not improve hypothyroidism, atopic dermatitis, anterior cruciate ligament rupture, or patellar luxation, and there was no exacerbation of symptoms. Laparotomy improved ceruminous adenoma. Therefore, it can be assumed that placental extract supplementation is unlikely to interfere in such cases with multiple diseases, suggesting that it can be used in similar cases.

Common treatments for corneal damage include the administration of hyaluronic acid, and antibiotics eye drops. Depending on the situation, antibiotics drugs may be administered orally or via injection. In the present two cases, eqPE was used as a supplement; therefore, it was ingested rather than administered as drops. eqPE is provided in liquid form, and if its safety and efficacy as an ophthalmic solution are confirmed, it could be administered as eye drops. Coenzyme Q10 was administered as eye drops to a patient with corneal damage in a previous case (Gumus, 2017), suggesting that the use of eqPE as eye drops is realistic. However, animals are reluctant to receive eye drops in many cases, and the administration of eye drops is burdensome for owners, except when visiting a doctor. eqPE can be ingested as if it were food or a snack, which reduces the psychological burden on veterinarians, owners, and the animals reluctant to receive eye drops. Therefore, eqPE supplementation is highly practical.

A limitation of this report is that no definitive diagnosis was made for the cases. To make a definitive diagnosis for this case, it is necessary to visit an ophthalmologist who has testing equipment. However, the owners of these cases did not want a definitive diagnosis because of the time and expense involved in testing, and because such veterinary clinics were located far away, making it difficult to visit them. In this way, we have seen that unconfirmed diagnoses due to psychological or physical reasons on the part of patients and their owners are emerging as a real problem and that there are effective therapeutic drugs and supplements that can be used safely even in such circumstances. Developing these is a challenge for the future, and placenta extract has the potential to become one.

To summarise, improvement of refractory canine corneal damage following the administration of placental extract supplementation was confirmed in the present two cases. However, as the number of cases was limited to two, more cases must be collected in the future. Further clinical trials with controls are required to confirm the efficacy of placental extract supplementation.

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Conflict of interest

Tadashi Nakagaki and Miwa Nakari declare that they have no competing interests. Kentaro Tahara, and Eiichi Hirano are employees of the Japan Bio Products Company Ltd.

Authors' contributions

MN and TN conceived and designed the clinical study, analyzed, and interpreted the data. KT wrote the first draft of the manuscript, analyzed, and interpreted the data. EH analyzed and interpreted the data and wrote the manuscript. All the authors approved the final draft of the manuscript.

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Data availability

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

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