

## Continuous ophthalmic treatment using an osmotic pump in a bull calf following surgical removal of an ocular dermoid: a case report

J.H. BAE<sup>1</sup>, C.E. PLUMMER<sup>2</sup>, J. KIM<sup>1</sup>, M.S. KIM<sup>1</sup>, N.S. KIM<sup>1</sup>

<sup>1</sup>College of Veterinary Medicine, Chonbuk National University, Jeonju, Republic of Korea

<sup>2</sup>Small Animal Clinical Sciences, University of Florida, Gainesville, USA

**ABSTRACT:** An intact male, six-month-old Hanwoo bull calf (native Korean beef breed) was presented to the Animal Medical Centre, Chonbuk National University because the owner had noticed a conjunctival and corneal abnormality in the left eye (OS). On ophthalmic examination, a small, elevated and skin-like mass lesion, containing hair was found on the ventronasal cornea and the conjunctiva of the third eyelid. In the light of its characteristic appearance, the lesion was classified clinically as a corneal dermoid. Under general anaesthesia, superficial lamellar keratectomy and conjunctivectomy was performed to remove the abnormal tissue. As the owner could not apply topical medications regularly, a drug-filled osmotic pump (Alzet; Alza, Palo Alto, CA) was implanted subconjunctivally under the upper eyelid and connected to a catheter at the lateral limbus. The catheter was fixed to the conjunctiva with 3-0 polyglactin 910 (Vicryl®; Ethicon, Johnson and Johnson, Somerville, USA) and a partial temporary tarsorrhaphy was placed. In order to determine the efficacy of medication delivery, a sample of aqueous humour was collected via aqueocentesis from the anterior chamber at two weeks and four weeks after implantation of the pump. The presence and concentration of ciprofloxacin was determined via mass spectroscopy. Aqueous concentration of ciprofloxacin was 0.093 µg/ml at two weeks and 0.107 µg/ml at four weeks. The calf healed without incident and returned to normal function six weeks following the procedure.

**Keywords:** calf; topical antibiotics; aqueous humour; keratectomy

Ocular dermoids, as reported, are peculiar defects characterised by normal tissue in an abnormal location, usually skin or skin-like masses of tissue arising on the limbus, conjunctivae, and cornea and occasionally on the eyelids (Gelatt 1981; Barkyoub and Leipold 1984; Neumann 1984; Yeruham et al. 2002). They are typically benign and non-progressive; however, they are a source of irritation which can usually be easily addressed by superficial lamellar keratectomy and/or conjunctivectomy and then supportive care while the surgical defect heals (Gelatt 1971). Post-operative medical therapy typically consists of topical antibiotics to prevent infection of the surgical wound and other topical and/or systemic medications to control pain and inflammation as needed. However,

the post-operative topical treatment of cattle is difficult because of poor patient and farm compliance and the frequency of topical medical therapy necessary. It can also be very stressful for cattle to undergo frequent therapy which can increase the danger to the handler.

In order to solve the problem of frequent medication administration in this bull calf, we employed an osmotic pump to deliver topical ciprofloxacin to the eye following surgical removal of the ocular dermoid. An osmotic pump is a delivery system for delivering drugs or other topical agents at a continuous and controlled rate (Theeuwes 1975). It delivers the agent via the osmotic pressure difference between compartments within the pump, called the osmotic layer, and the tissue environ-

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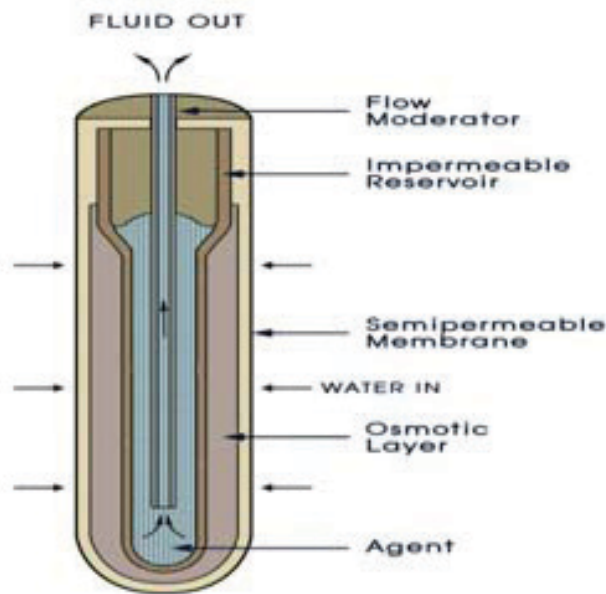


Figure 1. Illustration of the operation of the osmotic pump. When the osmotic pump is exposed to an aqueous environment, the osmotic layer imbibes water through a semipermeable membrane which forms the outer surface of the pump. The imbibed water compresses the impermeable reservoir, which collapses and displaces the contents from the pump at a controlled, predetermined rate

ment in which the pump is implanted (Figure 1). That is, when the osmotic pump is exposed to an aqueous environment, the osmotic layer imbibes water through a semipermeable membrane which forms the outer surface of the pump. The imbibed water compresses the flexible impermeable reservoir, which collapses and displaces the contents from the pump at a controlled, predetermined rate (Theeuwes and Yum 1976). Pumps such as the one used here have been used at a variety of sites including the spinal cord, spleen, liver, organ or tissue transplants, and wound sites (Eldridge et al. 1990; Xu et al. 1995). Despite their use elsewhere in the body, there are only a few reports regarding the use of osmotic pumps for delivery of medication to the eye (Blair et al. 1999; Ambati et al. 2000). However, these earlier studies revealed the potential usefulness of the osmotic pump for ocular diseases.

### Case description

A six-month-old intact male Hanwoo bull calf (native Korean beef breed) was presented to the Animal Medical Centre, Chonbuk National University after

the owner noticed a conjunctival and corneal abnormality in the left eye (OS). On ophthalmic examination, a small, elevated and skin-like mass, containing hair was found on the ventronasal cornea and the conjunctiva of the third eyelid (Figure 2). Ocular irritation, mild blepharospasm, and epiphora were evident. In both eyes, menace response and ocular reflexes were present, and Schirmer tear test values were 17.2 mm/min (OS), 16.4 mm/min (OD) and intraocular pressure values were 24 mmHg (OS) and 23 mmHg (OD). Fluorescein test was negative and aqueous fluid was clear on slit lamp examination. In the light of its characteristic appearance, the lesion was classified clinically as a corneoconjunctival dermoid. Given the irritation and discomfort caused by the mass, surgical removal of the lesion under general anaesthesia was planned.

The calf was anaesthetised with intramuscular injection (*i.m.*) of Zoletile® (2 mg/kg, Virbac, Carros cedex, France) and xylazine (0.05 mg/kg, Bayer Korea, Seoul, Korea). Local anaesthesia was induced using cotton swabs with 0.5% proparacaine hydrochloride (Alcaine; Alcon, Fort Worth, TX) applied directly to the surgical site. The eye was prepped routinely. Using a EL-5700 scleral blade (Eagle Laboratories Inc, Rancho Cucamonga, CA) and electrocautery (Cautery High Temp 2200 °F, Jorgensen Laboratories Inc, Loveland, Co), superficial lamellar keratectomy (at a depth of about one third of the cornea) and conjunctivectomy was performed with a surgical loupe ( $\times 4$  magnification) to remove the offending tissue as has been previously described (Figure 3a,b) (Shaw-Edwards 2010). The resultant wound bed was left open to heal by second

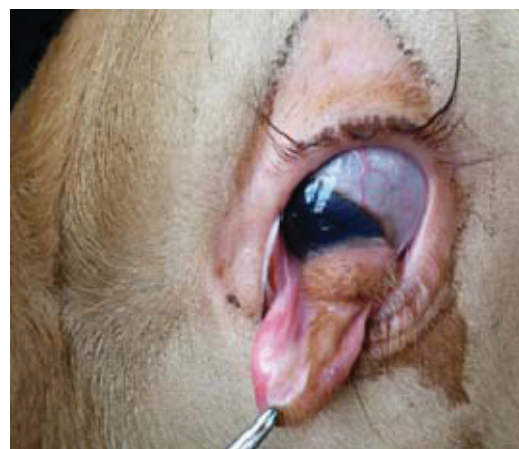


Figure 2. On ophthalmic examination, a small, elevated and skin-like mass, containing hair was found on the ventronasal cornea and the conjunctiva of the third eyelid

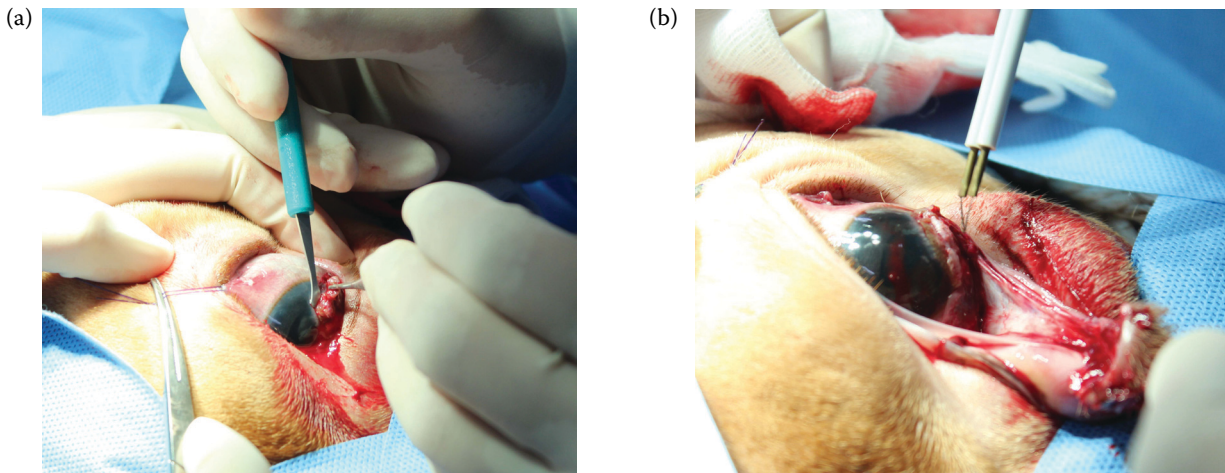


Figure 3. Using a EL-5700 scleral blade (a) and electrocautery (b), superficial lamellar keratectomy (a depth of 0.2–0.3mm) and conjunctivectomy was performed to remove the offending tissue

intention. Since the owner could not apply topical antibiotics regularly, we employed an osmotic pump (ALZET; ALZA, Palo Alto, CA) in order to administer topical medications. The osmotic pump was filled with 200  $\mu$ l 0.3 % ciprofloxacin (Cipex<sup>®</sup>, Samil, Seoul, Korea) using a syringe and a blunt-tipped filling unit and the flow moderator of the pump was then inserted. A translucent cap (Figure 4a) on the flow moderator was removed to expose a piece of the flow moderator (Figure 4b) which would connect to the catheter later according to the manufacturer's instructions. The pump was incubated in sterile saline at 37 °C for 40 h prior to implantation. All of these steps were performed in a laminar flow hood using sterile technique.

After a lateral canthotomy (1 cm) with a straight blunt-ended scissor, an incision (1 cm) was made through the conjunctiva of the upper eyelid with a tenotomy scissor and the osmotic pump was pre-loaded with antibiotic (Figure 5a) and then im-

planted subconjunctivally (Figure 5b). The pump was connected to the lateral limbus using a catheter (Polyethylene; ALZA, Palo Alto, CA) with an inside diameter of 0.76 mm (Figure 5c). The tip of the catheter was heated briefly using an alcohol lamp before fixation to the conjunctiva. The catheter was fixed with 3-0 polyglactin 910 (Vicryl<sup>®</sup>; Ethicon, Johnson and Johnson, Somerville, USA) using two simple interrupted patterns at intervals of 0.5 cm along the palpebral conjunctiva of the lower eyelid. Following implantation and fixation of the pump and catheter, three partial temporary tarsorrhaphy sutures of 4-0 nylon (Ethilon; Ethicon, Somerville, NJ) were performed, leaving the area of the medial canthus open. The sutures were tied with one end left long. The lateral canthotomy was closed with a figure-eight suture using 3-0 nylon (Ethilon; Ethicon, Somerville, NJ).

In order to assess the efficacy of delivery of drug to the eye, samples of aqueous humour were acquired via aqueocentesis to establish the presence and concentration of the drug in the anterior chamber. The drug used in this case to prevent infection of the surgical wound bed was ciprofloxacin, a fluoroquinolone known for its superior ability to penetrate the cornea and accumulate at sufficient levels in the anterior chamber. To measure the concentration of ciprofloxacin, 0.1 ml of aqueous humour was collected from the anterior chamber using a 30 g needle and a 1 ml syringe at two weeks and four weeks while the calf was under general and topical anaesthesia as for the keratectomy. The collected samples were stored at –70 °C until the assay could be performed. The tarsorrhaphy and figure-eight suture were removed two weeks

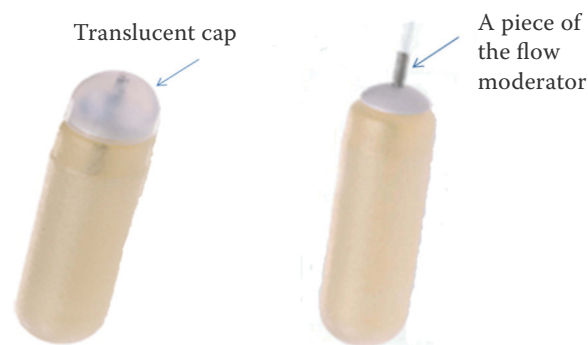


Figure 4. A translucent cap (a) on the flow moderator was removed to expose a piece of the flow moderator (b) which would connect to the catheter later



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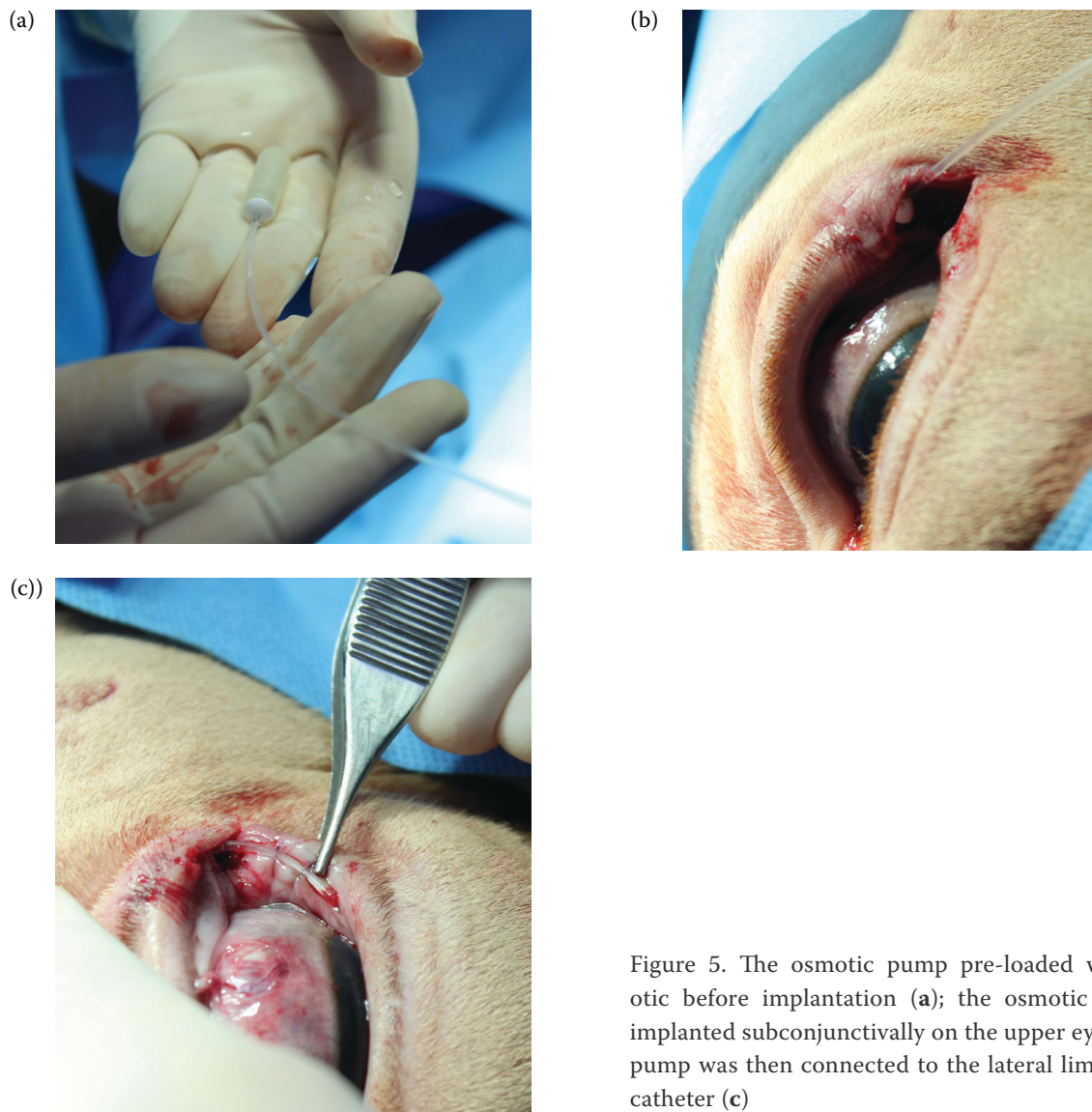


Figure 5. The osmotic pump pre-loaded with antibiotic before implantation (a); the osmotic pump was implanted subconjunctivally on the upper eyelid (b); the pump was then connected to the lateral limbus using a catheter (c)

following the initial procedure (at the time of the first aqueous humour collection) and the osmotic pump was removed four weeks post-operatively (at the time of the second aqueous humour collection). The calf recovered appropriately after each of his anaesthetic events and healed well following surgery. Six weeks postoperatively (Figure 6), the calf was comfortable and there was no evidence of residual irritation or epiphora. It then returned to its normal functions without restriction.

Ciprofloxacin was detected in the aqueous humour, demonstrating that the osmotic pump was able to deliver topical medications to the eye. The concentration of ciprofloxacin in aqueous humour was measured following chromatographic separation and mass spectrometric detection using a pro-

cedure adopted from Cantor et al. (2001) Aqueous concentration of ciprofloxacin was  $0.093 \mu\text{g/ml}$  at two weeks and  $0.107 \mu\text{g/ml}$  at four weeks. The residual volume of agent in the pump reservoir was also measured following removal. A filling tube attached to the syringe was used to aspirate the remaining agent from the pump reservoir according to the manufacturer's instructions. However, the residual volume in the reservoir was too low to measure its pure weight using a filling tube. Therefore, the osmotic pump was weighed before and after aspirating the agent several times for drying by using a filling tube and syringe. The weight of the osmotic pump was  $2.302 \text{ g}$  (before aspiration) and  $2.285 \text{ g}$  (after aspiration). Therefore, the residual volume of agent was  $17 \mu\text{g}$  following removal.



Figure 6. At follow-up 6 weeks after the keratectomy and conjunctivectomy, the surgical wound had healed appropriately, no ocular irritation or discomfort was observed and the calf had returned to its normal activities

## DISCUSSION AND CONCLUSIONS

To the authors' knowledge, this is the first reported case of the use of an osmotic pump for continuous administration of antibiotic solution after superficial keratectomy in a Bovid. For long-term treatment of ocular disorders in large animals, especially horses, subpalpebral lavage catheters (SPL) are used routinely to deliver topical solutions to the eye (Rebhun 1979; Abrams and Brooks 1990). However, even though these devices dramatically enhance topical ocular therapy, they still require the physical instillation of topical solutions through the system at regular intervals and are usually used for pulse therapy, rather than continuous delivery. This necessitates frequent handling of patients, which is impractical when treating cattle. There is an automated constant rate fluid delivery pump available that has been used in combination with an SPL in the horse (Myrna and Herring 2006). This external installation pump is replenishable and designed to deliver an agent at a predetermined rate (0.02–4.0 ml/h) for up to seven days. However, seven days of infusion is often insufficient to complete a course of treatment and it can be difficult to replenish the drug reservoir in an animal that is not handled regularly, such as a beef bull. These external installation devices can be easily broken or dislodged by animals that are not stalled and/or that are housed in groups. Subconjunctival implanted pumps have been described for continuous ocular treatment in horses (Blair et al. 1999). However, these pumps, too, have limited duration of delivery (seven days) and a very

limited capacity (100  $\mu$ l). Additionally, implants that are inserted into the subconjunctival space without an egress such as a catheter will not deliver drug to the corneal surface and therefore are not suitable for treatment of corneal epithelial diseases. The pump used in this case had a reservoir of 200  $\mu$ l and was designed to deliver a continuous rate of 0.25  $\mu$ l/h for four weeks. This pump with lavage catheter satisfied the requisite duration of infusion time and stability of installation for appropriate post-operative treatment of this bull calf.

It has been reported that the mean aqueous concentration after topical administration of 0.3 % ciprofloxacin is  $0.15 \pm 0.11$   $\mu$ g/ml (range 0.09–0.58  $\mu$ g/ml) in humans and 0.17  $\mu$ g/ml (range 0.09–0.95  $\mu$ g/ml) in dogs (Solomon et al. 2005; Yu-Speight et al. 2005). The aqueous concentration of ciprofloxacin (0.093  $\mu$ g/ml at two weeks and 0.107  $\mu$ g/ml at four weeks after implantation) was lower than that previously reported in humans and dogs. These concentration levels did not exceed the values (Table 1) for *Streptococcus* sp., *Staphylococcus* sp., *Corynebacterium* sp. and *E. coli* (Osato et al. 1989; Donnenfeld et al. 1994; Cekic et al. 1999). These results suggest that filling the pump with a high concentration of ciprofloxacin is necessary to reach comparable effectiveness for topical administration. However, it is clear that the osmotic infusion pump maintained the aqueous concentration of ciprofloxacin at a reasonable steady state until its removal four weeks after implantation. The amount of drug remaining in the pump was about 17  $\mu$ g/ml after four weeks. This also demonstrates the reliability of the pump. Connecting an ocular catheter to the pump can be associated with complications, such as eyelid abscesses and corneal ulcers (Friedman et al. 1989). However, in the current case, no complications with the catheter or its connection to the pump were observed. In conclusion, the current case indicates that an

Table 1. Ciprofloxacin MIC<sub>90</sub> values for canine aqueous humour organisms commonly reported as ocular contaminants in dogs

Organism	Ciprofloxacin MIC <sub>90</sub> ( $\mu$ g/ml)	References
<i>Staphylococcus</i> sp.	0.5	Theeuwes and Yum 1976; Yeruham et al. 2002
<i>Streptococcus</i> sp.	2	
<i>Corynebacterium</i> sp.	0.5	Xu et al. 1995
<i>Escherichia coli</i>	$\leq 0.25$	

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osmotic pump may be an effective treatment device for ocular disease in group-housed large animals.

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Corresponding Author:

Namsoo Kim, Chonbuk National University, College of Veterinary Medicine, 567 Baekje-daero, Jeonju, 561-756, Republic of Korea  
E-mail: namsoo@jbnu.ac.kr