Electrochemotherapy: an innovative treatment for cancer

Francisco Miras MVB, veterinary oncologist at Vet Referral, presents a case report on oncological cases treated using electrochemotherapy. The purpose of this article is to present the results obtained through this technique and to highlight its extensive benefits.

Background

The objective of the following case report is to consolidate the already-known clinical effectiveness of electrochemotherapy (ECT) in veterinary oncology. Several oncology cases treated with ECT have been selected in Vet Referrals, Galway, Ireland.

The use of ECT in veterinary medicine to treat tumours has spread significantly in recent years. The successful results obtained in the studies made ECT an interesting treatment line for the oncology clinic. In both human and veterinary medicine, ECT has been shown to be a highly effective local therapy for treating cutaneous and subcutaneous tumours.

Electrochemotherapy

Electrochemotherapy (ECT) is an innovative therapeutic modality for the treatment of tumors of any histological type. In recent years, significant advancements have been made, and its use is causing a major revolution in veterinary oncology (1,3,10).

ECT involves the application of electrical pulses to tumor cells pores in the cell membrane (permeabilization), allowing the introduction of cytostatic agents into the cell's interior with the aim of achieving a therapeutic effect, resulting in a process known as mitotic death (2,4,7).

Figure 1: Small needles electrode used for ECT.

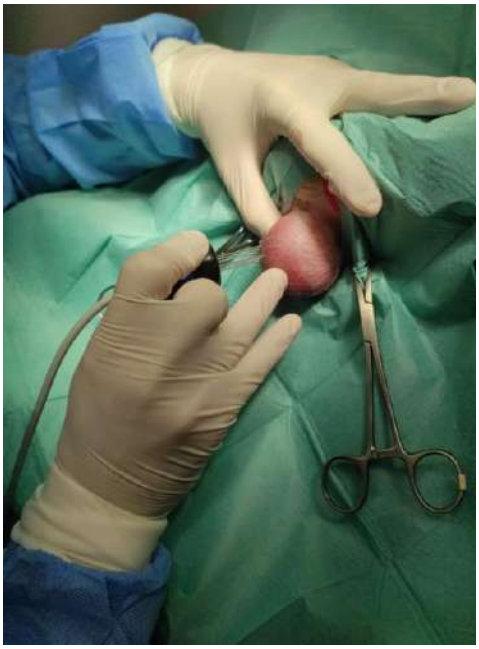

Figure 2: Application technique of ECT.

Differences between ECT and conventional chemotherapy

In ECT, unlike conventional chemotherapy, treatment is selectively targeted to the tumor, where the drug employed only enters the electroporated cells and not the rest of the cells. Therefore, ECT has minimal systemic side effects (2,16). Some patients may develop local inflammation or edema after application, but these adverse effects are usually mild and transient and do not have serious consequences for the patient.

One way to understand the fundamentals of ECT is to understand the mechanism of action of one of the most commonly used drugs in ECT, bleomycin. Bleomycin is a non-permeable cytotoxic drug that cannot diffuse through intact cell membranes. Without access to the cell's cytosol, bleomycin cannot reach the nucleus, where it exerts its effect. Therefore, under normal conditions where the cell's plasma membrane is intact, bleomycin cannot enter the interior of the cell and, consequently, has no effect on the cell. In contrast, if the cell is electroporated beforehand, creating pores in the cell membrane, bleomycin gains access to the cell's cytosol and subsequently to the nucleus, where it exerts its effect and causes cell death (6,15).

In this way, with ECT, we avoid the potential unwanted side effects that conventional chemotherapy can cause by affecting sensitive organs with a high rate of replication, such as the digestive system and the bone marrow.

Furthermore, patients previously treated with systemic chemotherapy and who did not respond satisfactorily can be treated with ECT, as it is a physical procedure that affects any cell type (regardless of histological type), and because the cytotoxicity of bleomycin is not affected by multidrug resistance mechanisms (as is the case with many types of tumors) (3,16)

Other beneficial effects

ECT has other beneficial effects for tumour control beyond the antitumor effect of the drug once it enters the cell. ECT also favours the immune response of the patient and causes a physiological reaction from electroporate tissue that tends to tumour control (6,7,8).

Another prominent effect is the phenomenon of "vascular lock", consisting of the vasoconstriction of the blood vessels of the electroporate zone inducing a transient and reversible reduction of blood flow thus allowing the greater retention of the drug in the tumor tissue and therefore a greater exposure of the agent to the tumor cells, in addition to vascular disruption due to the death of endothelial cells in the tumor vessel. This effect also reduces and prevents bleeding immediately after applying electrical pulses (5,8,17). In tumours such as mast cells that release histamine and other vasoactive substances into the bloodstream, the "vascular lock" prevents the release of granules and their possible complications (12,17).

Indications

The primary indication for ECT is the treatment of cutaneous and subcutaneous tumors. Other indications include the treatment of tumors in the oral and nasal cavities, and in recent years, significant advancements have been made in veterinary medicine for its application in other organs such as the bladder, urethra, liver, kidney, bone, and even the brain.

The general indications for the treatment of tumors with ECT are:

- As a first-line treatment for cutaneous or subcutaneous tumors (primary or metastatic) of any histology that cannot be satisfactorily treated with other therapeutic options.
- In combination with surgery for the treatment of cutaneous or subcutaneous tumors (primary or metastatic) of any histology in cases where complete margins cannot be guaranteed.
- Treatment of multiple presentation cutaneous or subcutaneous tumors where surgery could involve extensive resection areas.
- For the treatment of oral or nasal cavity tumors, either as a single therapy or in combination with surgery.
- For the treatment of surgical beds and/or margins in surgeries where the tumor has been incompletely resected.
- As a palliative measure in the treatment of primary or metastatic tumors that affect the patient's quality of life due to bleeding, ulceration, or pain.

Case presentation

Below, various cases of patients treated with ECT as a first-line treatment, ECT combined with surgery, and post-surgical application of ECT on surgical margins are presented. None of the cases presented below had regional or distant metastasis at the time of treatment.

- <u>ECT as a first-line treatment</u>

This application consists of the application of ECT as the sole treatment therapy.

Case 1. Feline patient with squamous cell carcinoma in the nasal plane. Complete response.

Figure 3. Image before the application of ECT.

Figure 4. Image 3 weeks after the application of ECT. Complete response.

Case 2. Feline patient with squamous cell carcinoma in the nasal plane. Complete response.

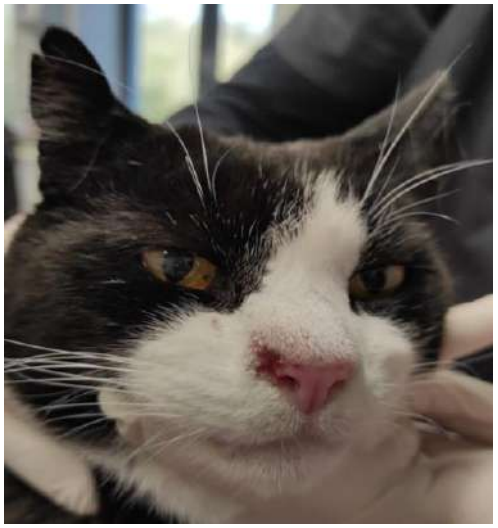

Figure 5. Image before the application of ECT.

Figure 6. Image 2 weeks after the application of ECT. Complete response.

Case 3. Feline patient with periocular squamous cell carcinoma. Complete response.

Figure 7. Image before the application of ECT.

Figure 8. Application of ECT.

Figure 9. Image 5 weeks after the application of ECT. Complete response.

Case 4. Feline patient with periocular squamous cell carcinoma. Complete response.

Figure 10. Image before the application of ECT.

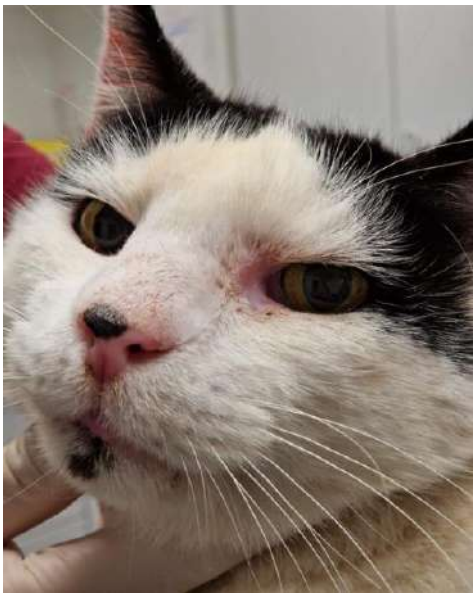

Figure 11. Image 4 weeks after the application of ECT. Complete response.

Case 5. Canine patient with a palpebral mast cell tumor. Complete response

Figure 12. Image before the application of ECT.

Figure 13. Image 4 weeks after the application of ECT. Complete response.

Case 6. Canine patient with oral melanoma. Complete response.

Figure 14. Image before the application of ECT.

Figure 15. Image 4 weeks after the application of ECT. Complete response.

Case 7. Patient with feline sarcoid in the paw. Complete response.

Figure 16. Image before the application of ECT.

Figure 17. Image 3 weeks after the application of ECT. Complete response.

Case 8. Female dog with a perineal hepatoid cell adenoma. Complete response

Figure 18. Image before the application of ECT.

Figure 19. Patient 6 weeks after the application of ECT. Complete response.

- Electrochemotherapy combined with surgery

This approach is indicated for the treatment of tumors where ECT as a single therapy may not guarantee promising results and where surgery does not allow for extensive approaches to achieve appropriate surgical margins. Therefore, in these patients, we combine electrochemotherapy with surgery.

To do this, we first perform a surgical approach to remove the tumor, followed by the application of ECT on the surgical bed to treat the margins and reduce the risk of tumor recurrence. Generally, we perform reconstructive surgeries such as skin flaps or skin grafts to correct the surgical defect produced by the surgery.

This combination allows us to treat tumors that would normally pose a significant surgical challenge with a high risk of recurrence. Furthermore, one of the main benefits is that the patient is treated with ECT on the same day as the surgery, making the procedure completed in a single visit.

Below, we present the treatment of different tumors located in anatomically challenging areas for surgical approaches, using surgery and electrochemotherapy.

Case 9. Canine patient with a soft tissue sarcoma (Grade II) on the lateral part of the carpus treated with surgery and intraoperative electrochemotherapy. A skin graft was performed during the same procedure. The patient is disease-free and has not developed tumor recurrence 9 months after the procedure was performed.

Figure 20. Image before the surgery and the application of ECT.

Figure 21. Image after the complete recovery of the patient. There is no tumour recurrence.

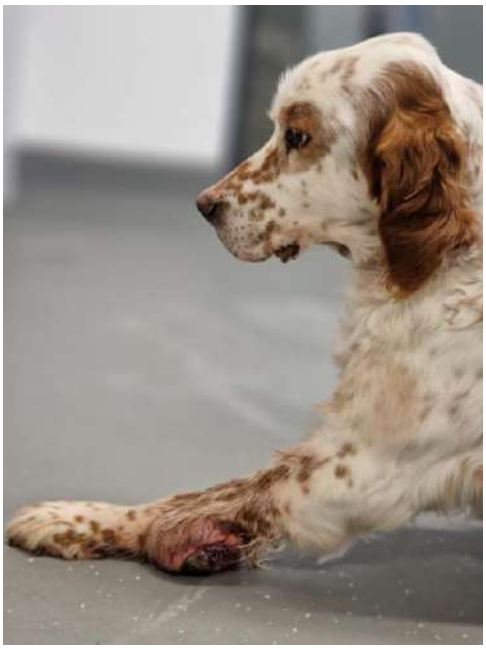

Figure 22. Image before the surgery and the application of ECT.

Figure 23. Image after the complete recovery of the patient. There is no tumour recurrence.

Case 10. Canine patient with a soft tissue sarcoma (Grade II) in the elbow treated with surgery and intraoperative electrochemotherapy. A skin flap was performed for the closure of the surgical defect. The patient is disease-free and has not developed tumor recurrence 12 months after the procedure.

Figure 24. Image before the surgery and the application of ECT.

Figure 25. Image after the surgery and the application of ECT.

Figure 26. Image after the complete recovery of the patient. There is no tumour recurrence.

Case 11. Canine patient with soft tissue sarcoma (Grade I) in the knee treated with surgery and intraoperative electrochemotherapy. A skin flap was performed for the closure of the surgical defect. The patient is disease-free and has not experienced tumor recurrence 12 months after the procedure.

Figure 27. Image before the surgery and the application of ECT.

Figure 28. Image during a post-operative check 4 weeks after the surgery and the application of ECT. Complete recovery of the patient.

Case 12. Canine patient with subcutaneous mast cell tumour on the lateral part of the carpus treated with surgery and intraoperative electrochemotherapy. A skin graft was performed during the same procedure. The patient is disease-free and has not developed tumor recurrence 8 months after the procedure was performed.

Figure 29. Image before the surgery and the application of ECT.

Figure 30. Image after the complete recovery of the patient. There is no tumour recurrence.

Case 13. Canine patient with a recurrence of ameloblastoma. Tumor excision and electrochemotherapy application were performed on the surgical bed. The patient is disease-free 3 months after the procedure and has not experienced a recurrence. The image shows the application technique.

Figure 31. Image before the tumor exeresis and ECT application.

Figure 32. Application of ECT on the surgical bed following tumor excision

- Post-surgical application of ECT

Consisting of the postoperative application of ECT on surgical scars, where the tumor has been removed but the margins have not been wide or are affected. This technique allows us to treat the surgical margins and reduce the risk of recurrences.

Case 14. Canine patient underwent a marginal excision of a cutaneous mast cell tumor (grade 2 according to the Patnaik classification). The histopathological study revealed that the surgical margins were narrow. The patient was referred to our center for adjuvant ECT application on the surgical scar. The patient has shown no tumor recurrence and remains disease-free 10 months after the application of ECT.

Figure 33. Image one week after ECT application.

Figure 34. Image 1 month after ECT application. There is no tumour recurrence.

Case 15. Canine patient with a cutaneous hemangiosarcoma located in the nasal area. A partial excision of the tumor was performed for histopathological study, but the margins were affected. The patient was referred to our center for the application of ECT on the surgical bed. Below, we can observe the response to ECT just 3 weeks after application, showing a complete response.

Figure 35. Image before ECT application.

Figure 36. Image 3 week after ECT application. Complete response

Discussion and conclusion:

ECT is a therapeutic option with very promising results and should be considered a highly relevant treatment option in veterinary oncology.

It has proven to be a highly effective treatment for solid cutaneous and subcutaneous tumors, regardless of their histological type, and has shown to be a very safe technique for the patient with low side effects.

Currently, it is beginning to be considered one of the first-choice treatments for squamous cell carcinomas in the feline species, providing a more conservative therapeutic option with rapid patient recovery (11). Similarly, it is a highly effective technique for the treatment of squamous cell carcinomas in the canine species (14). However, as mentioned previously, ECT is a very effective treatment for tumors of any histological type. Cutaneous mast cell tumors are another type of tumor that has also shown very promising results with complete responses, especially those < 2 cm3 (12).

Its application can be carried out as a first-line treatment (single therapy), in combination with surgery, or as post-surgical adjuvant therapy.

The combination of ECT with surgery or the application of ECT at the surgical site as adjuvant therapy has proven to be of great help in the treatment of tumors with complex

anatomical locations where complete excision with margins is not possible. The use of ECT during surgery or after surgery as adjuvant therapy provides excellent advantages to avoid the risk of recurrence in tumors where histopathological study does not reveal free margins (9).

In our center, the combination of ECT with surgery is a widely used technique for the treatment of tumors where the surgical approach is limited due to their anatomical location, especially in places like the limbs or the head. The most represented histological group in this technique is the treatment of soft tissue sarcomas, but we also treat tumors of other histological types.

It is worth noting that electrochemotherapy should not replace other therapeutic options but should be considered as another treatment choice. For example, in case 13, the canine patient with ameloblastoma, the recommended therapeutic option was maxillectomy, considering the favorable prognosis of this procedure and its good surgical approach. However, this option was rejected by the owner, and therefore, tumor excision with electrochemotherapy application on the surgical bed was recommended, opting for a more conservative approach.

Other application modalities that we perform in our center include the use of ECT in intranasal tumors, intraurethral ECT application, and ECT application in intra-abdominal or intrathoracic tumors.

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