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First use of Cisplatin as Chemotherapy for Treatment of Surgically-Excised Cutaneous Squamous Cell Carcinoma in Dromedary Camels: A Preliminary Report

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ABSTRACT

The purpose of this study was to assess the benefits of using cisplatin as a chemotherapeutic agent in camels with squamous cell carcinoma (SCC) that were surgically treated with either a scalpel blade or an electrosurgical technique. Twenty adult camels with histologically confirmed SCC were randomly divided according to the method used for tumor removal into group 1 (n=10) using scalpel blade, group 2 (n=10) using electrosurgical technique. Five camels from each group were treated postoperatively with cisplatin. In group 1 treated with scalpel blade alone, all the 5 camels with SCC (100%) had tumor recurrence and died before the end of the experiment. In group 1 treated with scalpel blade with the use of cisplatin, recurrence was noticed in 4 out of the 5 camels (80%) with skin SCC and 2 out of the 5 camels (40%) died. In group 2 treated with electrosurgery alone, all the 5 camels with SCC (100%) had tumor recurrence and all died before the end of the experiment. However, in group 2 treated with electrosurgery with the use of cisplatin, recurrence was noticed in only 2 out of the 5 camels (40%) with skin SCC and only 1 out of the 5 camels (20%) died. The results of the present study show that in both groups of skin SCC, all tumors in camels treated with a scalpel blade or electrosurgically but without the chemotherapy cisplatin recurred and collapsed. However, recurrence in group 1 treated with cisplatin was not noted in 1 camel (20%) and 3 camels (60%) survived. Interestingly, in group 2 treated electrosurgically with the use of cisplatin, 80% of the camels survived and recurrence occurred only in 2 (40%) of the camels. The results of this study showed that 4 out of total 10 cases treated with cisplatin post-surgically continued to be alive for 12 months without tumor recurrence. In addition, this study showed that hemorrhage and tumor recurrences were less when using electrosurgical technique compared to sharp scalpel blade method. It was concluded that chemotherapy using cisplatin appeared to be effective postoperatively in camels with SCC especially if treated surgically with electrotherapy. Administration of cisplatin decreased the rate of tumor recurrence and increase the survival rate in the camels with cutaneous SCC. Although, this study is the first that use the chemotherapy cisplatin in camels with SCC, results are preliminary. Another study with large numbers of diseased camels is warranted.

Key words: Animals, Electrosurgery, Cancer chemotherapy, Cisplatin, Squamous cell carcinoma.

INTRODUCTION

In humans and animals, neoplasia is considered a very important disorder. It has been reported to be a principal etiology of death all over the world comprising 7.6 million deaths (approximately 13% of overall deaths) (Stewart and Wild 2014). In domesticated animals, severe economic losses are a result of the occurrence of tumors (Mohamed et al. 2004). According to the prevalence of tumors reported in some published articles, neoplasms are most common in cattle (0.23%), and uncommon in sheep (0.002%), goats (0.009%), and pigs (0.004%) (Tharwat et al. 2012).

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A study on camels found that the prevalence of tumors is 0.006%, with skin and subcutaneous tissues being the most commonly recognized neoplastic disorders (Al-Sobayil et al. 2018). The most common tumors in camels are squamous cell carcinoma, fibroma adenocarcinoma, leiomyoma, fibromyxosarcoma, angiosarcoma, schwannoma, renal cell carcinoma, granulosa cell tumor, lipoma, sertoli-leydig cell tumor, and microcystic adnexal carcinoma (Ali et al. 2013, 2018; Tharwat et al. 2017, 2018; Sadan et al. 2024). It was found in the last report that skin squamous cell carcinoma (SCC) is the most common type of neoplasia in camels (Al-Sobayil et al. 2018).

Chemotherapy is a commonly used therapeutic agents used to treat neoplasms. Of these drugs, cisplatin (*cis*-dichlorodiammineplatinum (II) or *cis*-DDP) is a major chemotherapeutic agent used on a wide range as anticancer agent in human medicine and also in animals. Cisplatin is a broad-spectrum antineoplastic drug that can be used for different kinds of tumors in humans including that affect ovary, testis, urinary bladder, cervix and lungs as well as neck and head cancers (Konstantakou et al. 2009).

Cisplatin has been used in veterinary medicine for management of different types of cancers in pets such as sarcoids (Bogaert et al. 2008), urinary bladder (Greene et al. 2007), skin neoplasia (Hewes and Sullins 2006) and also in different malignant tumors (Knapp et al. 1988). In equines, cisplatin has been used as anticancer drugs in different tumors such as hemangiosarcoma (Norton et al. 2023), gingival fibrosarcoma (Horbal and Dixon 2016) and cutaneous tumors (Théon et al. 1994; Hewes and Sullins 2006). Cisplatin as an intratumoral chemotherapy has also been used in horses in sarcoids, SCC and squamous cell papillomas (Théon et al. 1999). The aim of this study was to assess the benefits of using cisplatin as a chemotherapeutic agent in camels with cutaneous SCC that were surgically excised using a scalpel blade or electrosurgical technique.

MATERIALS AND METHODS

Ethical approval

The Committee of Animal Ethics, Research of Scientific Deanship, University of Qassim, Saudi Arabia approved the experimental design (No. AC-34-292).

Camels

Twenty adult camels with skin SCC were housed at the University Veterinary Hospital, Qassim University for a year. A complete record for each camel was prepared including physical examination and blood analysis.

Clinical experiment

The cases of SCC (n=20) were divided based on the surgical technique used to remove the tumors into two groups: group 1 using a surgical scalpel (n=10) and group 2 using electrosurgical (n=10). Three weeks after surgery, 5 camels from each group were treated with chemotherapy using cisplatin while the other 5 were left as control animals.

Blood sampling and determination of the hematobiochemical parameters

Two milliliters of blood were collected from each camel and placed in EDTA tubes. A veterinary hematology analyzer (VetScan HM5, Abaxis, California, USA) was used to immediately measure total white blood cells (WBCs), lymphocytes (Lym), neutrophils (NEU), monocytes (MON), eosinophils (EOS), red blood cell counts (RBCs), hematocrit (HCT), hemoglobin (HG), and RBC indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Surgical operation

A camel was controlled in a sitting or lateral position depending on the location of the SCC, and then sedated with xylazine (Ilum xylazil-20, Troy laboratories pty limited, Australia) at a dose of 0.1-0.2mg/kg IV. Local anesthesia using lidocaine 2% (Lidomic 2%, Laboratorios Microsules, Uruguay) was infiltrated around the tumor region. A bold elliptical skin incision using either scalpel blade (group 1) or electrosurgical device (DRE Citadel 300 Electrosurgical Unit, DRE, USA) (group 2) was performed around the area of tumor. Tissues around the tumor were dissected using either the scissors (group 1) or electrosurgical device (group 2) and then the tumor mass was surgically removed. Suturing was applied using polyglycolic acid NO 2 (SMI AG Steinerberg 8-4780ST.VITH-Belgium) for internal and silk NO 2(SMI AG Steinerberg 8-4780ST.VITH-Belgium) for external layers. Post-operative surgery included daily antibiotics (penicillin and streptomycin, 3mL/50kg bw, IM) for seven days and topical antiseptic spray on the wound. External sutures were removed 21 days post-surgery.

Chemotherapy

Chemotherapy using cisplatin was administered at 2-week intervals for 4 successive doses in 5 cases of each group of SCC cases. At the beginning, the animals were injected intravenously with 5L lactated ringer then cisplatin was diluted in 2L of 0.9% sodium chloride solution and given by slow infusion into the jugular vein over a period of 4-5 hours at a dose of 0.2mg/kg. Then another 5L of lactated ringer was given intravenously. Blood samples were collected weekly in EDTA tubes (for complete blood count) before and after the treatment using automated blood machines (VetScan HM5, Abaxis, California, USA).

Histopathology

Diagnosis of SCC for each tumor was carried out using histopathological analysis. Biopsies and specimens from surgically excised tumors were fixed in 10% buffered formalin and embedded in paraffin following standard procedures. Sections, 4 µm thick, were stained with (HandE) (Bancroft and Gamble 2007). Stained sections were examined under light microscope and photographed using digital camera.

RESULTS

Results showed that the severity of hemorrhage was less with electrosurgical technique compared to scalpel blade. A histopathological exam confirmed SCC in all 20 camels (Fig. 1). Recurrence of cancer occurred in all surgically-treated animal without administration of Cisplatin and they died within 4 months post-surgery (Table 1). A significant reduction in WBC, LYM, MON, EOS, RBC, HG and HCT post treatment compared to pre chemotherapy (Table 2) ($P<0.05$). The NEU concentrations were significantly higher post treatment compared to pre chemotherapy ($P<0.05$).

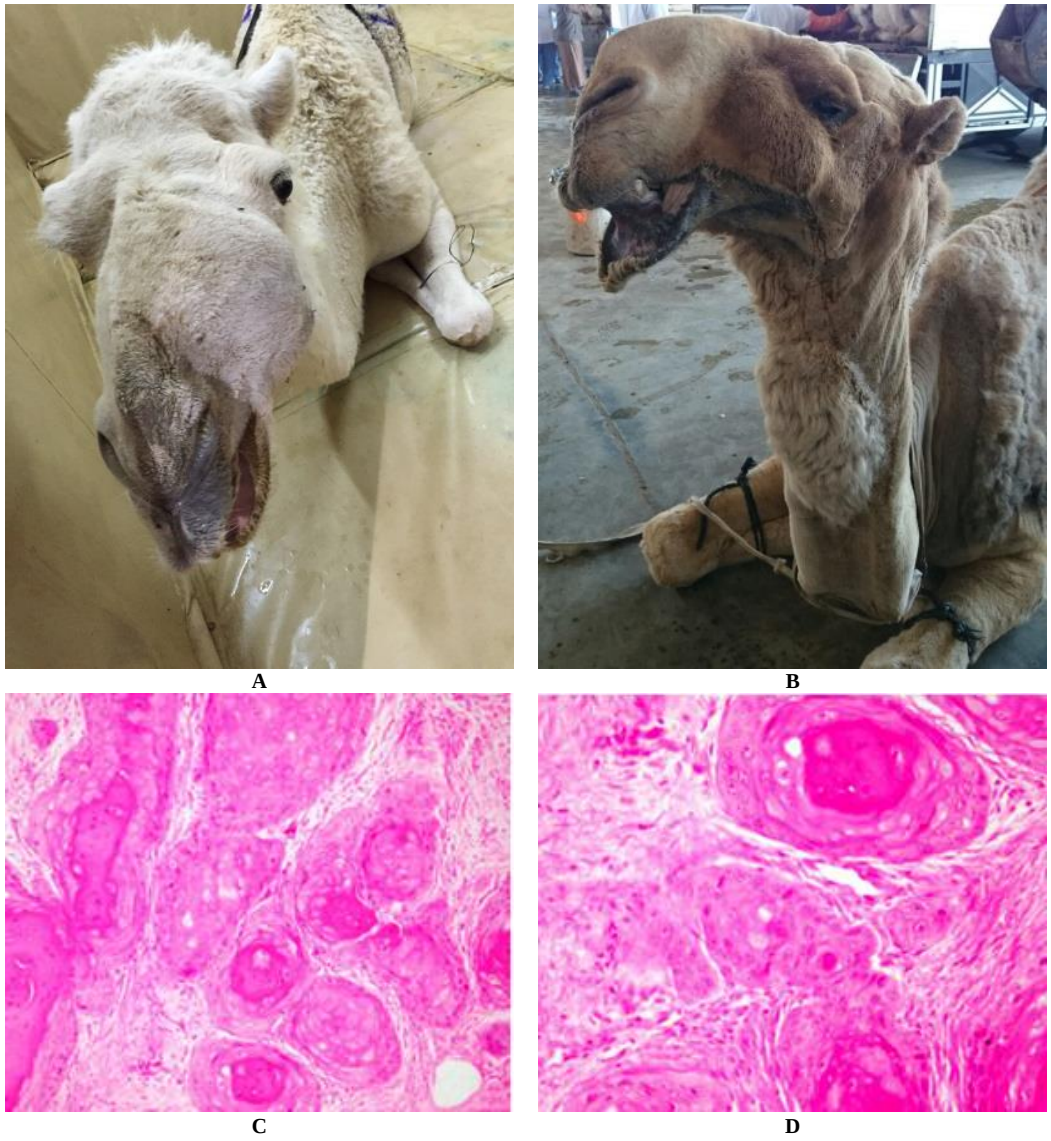

Fig. 1: Two camels with squamous cell carcinoma in the head (**A** and **B**). Images **C** and **D** show histopathological findings of squamous cell carcinoma revealing infiltrating well differentiated keratinizing squamous cell carcinoma multiple cell nests and keratin pearl formation (Hand E; **C** ×200; **D** ×400).

Table 1: Camels with squamous cell carcinoma treated surgically with regular sharp scalpel (Group 1) or electrosurgically (Group 2) techniques with and without chemotherapy

Group	With/out chemotherapy	Gender	Location of tumor	Tumor recurrence	Animal status
Group 1	Without Chemotherapy	Female	Sacrum	Recurrence	Die
		Female	Head	Recurrence	Die
		Female	Head	Recurrence	Die
		Female	Limb	Recurrence	Die
		Female	Rectum	Recurrence	Die
	With Chemotherapy (Cisplatin)	Female	Limb	No recurrence	Alive
		Female	Abdomen	Recurrence	Alive
		Female	Limb	Recurrence	Alive
		Female	Sacrum	Recurrence	Die
		Female	Abdomen	Recurrence	Die
Group 2	Without Chemotherapy	Female	Abdomen	Recurrence	Die
		Female	Head	Recurrence	Die
		Female	Limb	Recurrence	Die
		Female	Limb	Recurrence	Die
		Female	Limb	Recurrence	Die
	With Chemotherapy (Cisplatin)	Female	Head	Recurrence	Die
		Male	Head	No recurrence	Alive
		Female	Head	No recurrence	Alive
		Female	Head	Recurrence	Alive
		Female	Rectum	No recurrence	Alive

Table 2: Mean±SE of blood parameters for camels with squamous cell carcinoma pre and post chemotherapy infusion with regular sharp scalpel (Group 1) or electrosurgically (Group 2) techniques with and without chemotherapy

Parameter	Group 1		Group 2	
	Pre	Post	Pre	Post
WBCs ($\times10^9$/L)	12.12 ±3.1[a]	9.31±2.8[b]	11.98±2.8[a]	9.42±1.5[b]
Lymphocytes ($\times10^9$/L)	2.39±0.7[a]	0.74±0.5[b]	1.92±1.1[a]	0.83±0.4[b]
Monocytes ($\times10^9$/L)	0.23±0.2[a]	0.17±0.03[b]	0.13±0.02[a]	0.09±0.01[b]
Neutrophils ($\times10^9$/L)	7.95±1.6[a]	9.42±4.1[b]	8.3±2.7[a]	10.27± 3.6[b]
Eosinophils ($\times10^9$/L)	1.95±0.4[a]	1.31±0.3[b]	1.54±0.3[a]	0.13± 0.1[b]
RBCs ($\times10^{12}$/L)	9.11±2.3[a]	7.31±2.6[b]	10.11±2.2[a]	7.69± 2.1[b]
Hemoglobin (g/dL)	13.2±2.4[a]	11.1±2.2[b]	12.1±2.8[a]	10.4± 1.1[b]
Hematocrit (%)	19.11±4.2[a]	15.13±2.4[b]	18.33±3.1[a]	14.95± 2.3[b]
MCV (fL)	24±2.2[a]	24±1.3[a]	24±1.2[a]	23± 1.6[a]
MCH (pg)	16.2±1.3[a]	15.1±1.3[a]	15.1±1.4[a]	14.5± 1.1[a]
MCHC (g/dL)	63.2±4.4[a]	57.5±3.6[a]	61.7±4.3[a]	57.6± 3.2[a]

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration. Different superscripts differ significantly ($P<0.05$) between pre- and post-values in either group 1 or group 2.

In this study, camels in group 1 with SCC that was surgically excised with scalpel blade and without the use of cisplatin, all the 5 camels with SCC (100%) had tumor recurrence and died before the end of the experiment. In group 1 with SCC that was surgically excised with scalpel blade but with the use of cisplatin, recurrence was noticed in 4 out of the 5 camels (80%) with skin SCC and 2 out of the 5 camels (40%) died. In group 2 with SCC that was surgically excised with electrosurgery device and without the use of cisplatin, all the 5 camels with SCC (100%) had also tumor recurrence and all died before the end of the experiment. However, in group 2 with SCC that was surgically excised with electrosurgery device with the use of cisplatin, recurrence was noticed in only 2 out of the 5 camels (40%) with skin SCC and only 1 out of the 5 camels (20%) died. The current study's findings show that in both groups of skin SCC, all tumors in camels treated surgically but not with the chemotherapy cisplatin recurred, and all camels collapsed. However, recurrence in group 1 treated with cisplatin was not noted in 1 camel (20%) and 3 camels (60%) survived. Interestingly, in group 2 treated electrosurgically with the use of cisplatin, 80% of the camels survived and recurrence occurred only in 2 (40%) of the camels.

DISCUSSION

There are few reports describing the incidence of neoplasms in dromedary camels (Al-Sobayil et al. 2018). Although neoplasms of the skin and subcutaneous tissues are the most commonly recognized neoplastic disorders in domestic animals, skin neoplasms have been reported in camels in individual cases. Case reports of squamous cell carcinomas and basal cell carcinoma (Al-Hizab et al. 2007) have been described in camels.

In humans, neoplasia is treated through different regimes depending on the type and progression of the tumor. In today's world, there are essentially two ways to treat cancer: remove the tumor through surgery and create cancer-free edges all around the tumor, or destroy the tumor's ability to grow through radiation, chemotherapy, or both. Treatment may be only by one method but mostly a combination of surgical interference in line with radiation therapy and chemotherapy (Liu et al. 2021).

Cisplatin is used as a chemotherapeutic agent on a large scale in fields of human and veterinary medicine (Dasari et al. 2022). Neoplasia in camels leads to animal suffering and is usually fatal (Al-Sobayil et al. 2018). This study was therefore carried out to diminish camel pain and to show the treatment success rate of the chemotherapeutic agent cisplatin in camels with cutaneous SCC and recurrence and survival rates. To the authors' knowledge, this report is the first that document the usage of cisplatin as chemotherapy in camels with the skin neoplasia SCC.

This study has shown that chemotherapy with emphasis of cisplatin might be a useful drug to be used in camels with SCC. In humans, cisplatin is an effective drug that can be used to treat head and neck SCC (Marur and Forastiere 2016). One problem post cisplatin infusion in camels was the significant reduction in white blood WBC, LYM, MON) EOS, RBC, HG) and HCT. On the other side, NEU concentrations were significantly higher post treatment compared to pre chemotherapy. Although chemotherapy infusion showed a negative effect on blood hematological parameters, the intravenous fluids given pre and post chemotherapy might contribute in these changes in blood pictures.

Six months post-surgery, recurrence of tumors in camels with chemotherapy was 4/5 (80%), 2/5 (40%) in groups 1 and 2, respectively. In chemotherapy groups, 2/4 (50%) and 1/2 (50%) of camels with SCC recurrence died within 6 months in groups 1 and 2, respectively. At the end of the study (12 months), three camels from group 1 and 4 camels from group 2 were alive. Tumor recurrence was not detected in one camel (1 out of total 3 alive) belonging to group 1. In group 2, recurrence of tumor was not detected in 3 camels (3 out of total 4 alive). In dogs, the use of cisplatin to treat SCC, complete remission in 1 out of 11 dogs (9.1%). In addition, partial remission was found in 1 out of the 11 dogs with SCC (9.1%) (Knapp et al. 1988). In 27 horses and 1 mule with confirmed 32 skin tumors, it was reported that the intraluminal injection of cisplatin is effective and safe for special tumors especially if given at the peri-operative period (Théon et al. 1994). Théon et al. (1999), has also reported that intratumoral administration of the chemotherapy cisplatin is useful for medication of skin neoplasia in horses. Similar, it was suggested also that the intratumoral administration of cisplatin may be effective in equidae with different skin neoplasia (Hewes and Sullins 2006).

It can be concluded from this study that using cisplatin in camels after surgical removal of SCC with electrosurgery decreased the rate of tumor recurrence and increase the survival rate. Although, this study is the first that use the chemotherapy cisplatin in the treatment of neoplasia in dromedary camels, results are preliminary. Another study using large numbers of diseased camels is therefore warranted. Specific biomarkers for SCC should be evaluated before and after treatment. In addition, immunohistochemical markers (IHC) (p40, p63, CK5/6, and DSC3) as index tests for SCC and IHC slides to specify tumor cells should also be investigated.

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Conflicts of interest statement

The authors have no conflicts of interest to disclose.

Author contributions

Conceptualization and design: FA, MT, AA, AF and MK; Practical work: FA, MT, AA, and AF; formal analysis and interpretation of data: FA and MT; histopathological work: MK; writing-original draft preparation: FA and MT; review and editing: AA, AF and MK. The final manuscript was revised and approved by all authors for publication.

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