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Effects of cisplatin chemotherapy on the osseointegration of titanium implants☆

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ABSTRACT

Purpose: The effect of chemotherapy on the osseointegration of dental implants has received less interest compared with radiotherapy. Thus, the aim of the current study was to investigate the effect of cisplatin chemotherapy on the osseointegration of dental implants in a rabbit model.
Materials and methods: Sixteen New Zealand White rabbits were randomly assigned to two groups of treatment of either cisplatin at 2.5 mg/kg/week for 4 weeks (n = 8) or placebo (n = 8), in which the first dose was administered 2 days prior to the surgical procedure. Each rabbit received one titanium dental implant inserted in the right distal femoral condyle. Four rabbits from each group were sacrificed 4 and 8 weeks after implant insertion. Osseointegration of the dental implants was analysed using micro-computed tomography and histomorphometric evaluation.
Results: Analysis of micro-computed tomography data and histomorphometric data showed that the osseointegration parameters, including the ratio of bone volume to total volume (BV/TV) and bone-implant contact (BIC%) for the cisplatin group, were significantly lower compared to the control group at 4 and 8 weeks. ($P \leq 0.05$).
Conclusion: Cisplatin chemotherapy had a negative effect on the osseointegration of dental implants when inserted throughout the chemotherapeutic regimens in a rabbit model.

1. Introduction

Oral rehabilitation of cancer patients with dental implants has a positive effect on quality of life after reconstructive surgery of the jaw (Jacobsen et al., 2016). Bony reconstruction of the surgical defects is usually performed using the fibula or iliac crest free flap, in which dental implants are inserted within the same reconstruction procedure (Cuesta Gil et al., 2012; Nocini et al., 2012) or secondary to the grafting procedure (Kramer et al., 2005; Raoul et al., 2009).

Current advancements in computer-guided surgical planning have motivated surgeons to consider jaw reconstruction with simultaneous implant placement to achieve early functional rehabilitation (Urken et al., 1998; Odin et al., 2010; Nocini et al., 2012; Zavattero et al., 2015; Zhang et al., 2015).

Although such an approach allows osseointegration of dental implants to commence during the healing phase of the bone graft and before the beginning of radiotherapy, there might still be an overlap between the osseointegration process and the administration of chemotherapy, particularly in patients who would benefit from combined surgery and chemotherapy.

The effect of chemotherapy on implant survival has been discussed in two previous studies. Kovacs (2001) showed that chemotherapy in the form of cisplatin had no negative effect on implant survival over 10 years when the implant was placed, on average, 10.5 months after chemotherapy, whereas an earlier study that investigated root form implants with machined surface and blade type implants (Karr et al., 1992) recommended removal of the

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implants prior to chemotherapy. The studies presented opposing opinions about the effect of chemotherapy on implant survival and provided little knowledge on its effect on the primary osseointegration process.

Cisplatin is a well-known chemotherapeutic agent that is used as a mono-therapy or in combination with other anti-neoplastic drugs in the management of testicular, ovarian, bone, breast, bladder, head, and neck cancers (Pil and Lippard, 2002; Scholar, 2007; Kano et al., 2011). It inhibits both the replication and transcription of cellular DNA and induces programmed cell death (Scholar, 2007).

McDonald et al. (1998) reported a case of a 29-year-old woman who had four successfully osseointegrated implants that were inserted simultaneously with reconstruction prior to six cycles of adriamycin and cisplatin. Zart et al. (1993) concluded that chemotherapy with cisplatin had an unfavourable effect on bone healing in rats. Moreover, Monsell et al. (2013) concluded that chemotherapy using adriamycin and cisplatinum prior to distraction osteogenesis decreased the volume of the regenerated bone, without affecting the quality of the formed callus in a rabbit model. However, opposing results were obtained by Young et al. (1997a, 1997b). These authors concluded that preoperative cisplatin did not alter the formation of new bone around porous-coated titanium prostheses, but specimens from dogs treated after implant insertion with the same medication showed significantly less bone remodelling (Young et al., 1997b).

Such controversy with regard to the effect of such an important chemotherapeutic agent highlights the need for additional in-depth studies of the effect of cisplatin. Thus, the aim of the current study was to investigate the effect of cisplatin on the osseointegration process of dental implants inserted in a rabbit model using histomorphometric and micro-computed tomographic (micro-CT) analysis.

2. Materials and methods

2.1. Animals and ethics

The design of the current study was approved by the ethical review board for experimental animal research (approval no. IRB-2014-02-024). All animal procedures were performed according to the regulations and ethical guidelines of the international guiding principles for biomedical research involving animals (December 2012) as well as with the Standing Committee for Research Ethics on Living Creatures at our institute (SCRELC).

2.2. Study protocol

Sixteen adult male White New Zealand rabbits aged 6–9-months and weighing 3.5–4.5 kg were included in this study. Animals were provided by the experimental animal care centre at College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. Each rabbit was housed in an individual stainless steel cage with free access to a standard rabbit pellet diet and water. The housing room at the Laboratory Animal Unit was maintained under proper ventilation and automatically controlled conditions (25 °C, 50–55% relative humidity and 12 h of light followed by 12 h of darkness).

Following 2 weeks of acclimatization, rabbits were randomly assigned to two groups of either cisplatin (Hospira Australia Pty Ltd., Lexia Place, Mulgrave, Victoria 3179, Australia) at 2.5 mg/kg/week for 4 weeks ($n = 8$) or placebo ($n = 8$), in which the first dose was administered 2 days prior to the surgical procedure. The dose of cisplatin was selected on the basis of previous work (Wong et al., 1988). Cisplatin was administered as an intraperitoneal solution at a ratio of 1:2 with normal saline. The placebo group was administered the same volume of intraperitoneal normal saline solution.

2.3. Surgical procedure

Each rabbit received one titanium dental implant inserted in the right distal femoral condyle by the same experienced surgeon. The animals were anaesthetized by intramuscular injection of 30 mg/kg ketamine and 5 mg/kg xylazine. Preoperatively, intramuscular injections of 30 mg/kg of long-acting oxytetracycline (Troy Laboratories Pty Limited, Glendenning, NSW, Australia) and 1.5 mg/kg of diclofenac sodium (Novartis, Basel, Switzerland) were administered by a veterinarian.

The lateral surface of the right hind leg of the rabbit was shaved and washed, and the surgical site was then disinfected with iodine antiseptic solution and isolated with sterile surgical towels. Before skin incision, 1 ml of 2% lidocaine with 1:100:000 epinephrine (Novocol Pharmaceutical of Canada, Inc., Cambridge, ON, Canada) was injected for local anaesthesia and haemostasis. A skin incision of approximately 2 cm in length on the lateral surface of the right hind leg, blunt dissection of the muscles and reflection of the periosteum were performed to expose the flat bone surface on the lateral aspect of the distal condyle. The site for implant insertion was selected at the center of the head of the femur away from the lateral, medial, and distal edges to exclude the peripheral cortical bones at these areas (Fig. 1a). The implant site was sequentially enlarged with surgical drills with an increasing diameter according to the standard protocol of the manufacturer (SIC surgical kit, Schilli Implantology Circle, Germany) using a low rotational drill speed (800 rpm) under copious irrigation with sterile normal saline. Sixteen cylindrical screw-type titanium dental implants (SICmax® invent AG, Birmannsgasse 3, CH-4055 Basel, Switzerland) that were 3.7 mm in diameter and 7.5 mm in length were inserted into the distal condyle of the right femurs of the 16 rabbits. All of the implants were inserted unicortically (perpendicular to the flat bone surface) and threaded to the bone level, and cover screws were then inserted. Subsequently, the surgical sites were closed in separate layers with Vicryl 3-0 resorbable sutures (Ethicon GmbH, Norderstedt, Germany). Animals were then transported to the recovery room and observed for any potential complications until complete recovery.

Postoperative daily injections of 1.5 mg/kg of diclofenac sodium and 15 mg/kg of oxytetracycline were administered for 3 days, and the animals were observed for any signs of infection or wound dehiscence.

Four animals from each group were sacrificed 4 and 8 weeks after implant insertion by an overdose of pentobarbital (Narkorens, Meral GmbH, Hallbergmoos, Germany), and the femoral specimens were harvested. The femur-implant specimens were excised and sectioned using a diamond circular saw from 1 cm proximal to 1 cm distal to the implant, and the bone specimens containing the implants were subsequently fixed in 4% buffered formaldehyde for further micro-CT and histomorphometric evaluation.

2.4. Micro-CT analysis

Bone specimens containing the implants were scanned using the SkyScan 1172 desktop X-ray Micro-CT System (SkyScan, Kontich, Belgium). Before scanning, bone blocks containing the implants were wrapped in Parafilm M® (Pechiney Plastic Packaging, Chicago, IL, USA) to maintain the hydration of the bone during scanning. To obtain a standardized 3-dimensional (3D) analysis of the bone surrounding the titanium implants, the specimens were mounted vertically onto the sample holder with the long axis of