SUBMUCOSAL ADMINISTRATION OF DEXAMETHASONE FOR DENTAL IMPLANT SURGERY

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Abstract

Dexamethasone can reduce post-operative pain and swelling. An appropriate administration of dexamethasone for dental surgical procedures may be local submucosal infiltration. Local delivery may produce a faster onset with more drug at the desired site of action. A single submucosal dose will unlikely produce side effects.

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INTRODUCTION

Dental surgeons use local or systemic dexamethasone (DX) to minimize post-operative symptoms (Fig. 1) (1,2,3,4,5,6). DX can be administered topically, intramuscularly, intravenously, intra-alveolarly and submucosally (1,2,3,4,5,6). Local submucosal infiltration may be the best method to administer DX for appropriate minimization of postoperative pain, trismus and edema (1,2,3,4,5,6). While oral, intravenous or intramuscular administration is also appropriate, local administration is more convenient and performs equally well (1,2,3,4,5,6).

While previous work was done for post-operative third molar removal, DX may have applications in dental implant surgery.

A 4mg submucosal dose may the most efficacious since a higher dose has been shown to be of no benefit in third molar extraction (4,5,7).

PHARMACOLOGY OF DEXAMETHASONE

Dexamethasone is a glucocorticoid and is used to treat a multiplicity of diseases and disorders including arthritis, allergies, asthma, obstructive pulmonary diseases, croup, adrenocortical insufficiency among others (8). DX is an anti-inflammatory and immunosuppressant. It is 68% bound in plasma (9). It was approved for use by the Food and Drug Administration in 1961. It is listed on the World Health Organization's List of Essential Medicines. It is available for oral, topical, submucosal, intramuscular and intravenous administration. The effects generally occur within 24 hours and in as little as 10 minutes and can last up to three days (8). Long term usage may induce significant side effects such as candidiasis, bone loss, cataracts, hiccups and muscle weakness (8). It should only be used during pregnancy if the benefits out-weigh the teratogenic risks for use (FDA Category C) (8).

DX reduces prostaglandins and leukotrienes and blocks phospholipase A2 (4). DX is more potent than cortisol (4). DX can be administered orally, intra-alveolarly, submucosally, intravenously, and intramuscularly (4, 5).

4mg infiltrated locally at an oral surgical site can reduce pain, swelling and inflammation (4,5). Post-operative healing depends on inflammation and angiogenesis. This is a complex process and DX may inhibit

angiogenesis by inhibition of VEGF (10).

Since DX is not well studied for pregnant patients, the FDA has a rating of Category C. Nonetheless, a low dose may be safe but consultation with the patient's physician to evaluate the risk-benefit is appropriate (11).

The permeability of intra-alveolar administration of DX was evaluated*in silico* and found that its molecular characteristics would facilitate intra-alveolar administration (5).

DX is a potent anti-inflammatory agent with a long half-life of 36-72 hours when administered intramuscularly (9). There are side effects of DX, nonetheless, a short course of low dose therapy, in the absence of contraindications, is unlikely to be harmful (9). Patients with DX contraindications may not be appropriate for dental implant surgery. Careful preoperative evaluation is appropriate for every dental implant patient.

CLINICAL USEAGE

DX is commonly used to treat nausea and vomiting after general anesthesia (12). There is a dearth of evidence on drug safety, nonetheless, a single 4mg dose may not be detrimental (12). Nonetheless, carefull administration should be done to avoid injection into a blood vessel.

While there are several studies of DX for successful post-operative pain and trismus control, a systematic analysis showed that the evidence is inadequate to and beyond the seventh post-operative day (4). Nonetheless, several studies did find adequate pain and trismus control with submucosal DX (4). Thus, DX seems to be effective for early post-operative pain and trismus control, but this is yet to be confirmed with a systematic analysis (4).

Infiltration of DX in close proximity to the surgical site brings the drug close to the target and an increased dosage as compared to an oral dose (1,2,3,4).

DX combined with acetaminophen can reduce myalgia associated with acute phase response, following initial zoledronic acid treatment (13). A combination of pain relievers may increase the effectiveness of DX. However, DX combined with alendronate can increase the formation of necrotic bone by increasing the accumulation of macrophages. Thus, dental implant patients taking an alendronate may not be good candidates for DX administration (14). Accumulation of macrophages around an endosseous dental implant may induce an osseonecrosis (14). Additionally, patients taking DX for a few weeks may be prone to developing sequestra following tooth extraction especially if zolendronic acid is also being administered (15).

Orally administered DX has been used for postoperative pain and swelling and inflammation (4). This is usually taken for several days. However, low dose local submucosal administration may be as effective and convenient with fewer side effects (5).

Intra-alveolar administration of DX requires an open osseous wound. 4mg of the powder form of DX can be placed intra-alveolarly and can perform well to prevent edema and pain (5). This form of administration may be useful for osseous edentulous split ridges where there may be an osseous opening of the edentulous ridge and in osseous donor sites (Fig. 2). An open osseous wound that is not primarily closed may allow the powder to be washed out by blood and oral fluids. Thus primary closure may be necessary. A DX carrier made of a polymeric starch combined with polycaprolactone may be soon available for intra-alveolar delivery (16).

Because of its long half-life DX may be used as a depot drug for repeated submucosal injections at the surgical site if required (4).

Since DX is FDA Category C, the use of DX for dental treatment should benefit the patient more than the risk for teratogenic outcomes (8). Generally, the dosages used in implant dentistry would be small but there is no research that obviates this risk.

SIDE EFFECTS OF DEXAMETHASONE

Side effects include candidiasis, bone loss, cataracts, hiccups and muscle weakness but no studies have found severe complications with submucosal or intra-alveolar DX (4).

DX can inhibit platelet aggregation in rats (17). Rats were daily orally administered 1-4 mg/kg of DX for 5 days. Fibrolytic activity was decreased at 3mg/kg but not at 1mg/kg and yet arterial thrombosis was decreased at low doses. Platelet aggregation inhibition is counter-acted at higher doses because of decreased fibrinolytic activity (17). This was an in vivo study in rats, nonetheless, a single 4mg submucosal dose is 0.06mg/kg and is far below any suspected platelet action.

High doses of DX administered for long terms can cause mesenchymal stem cell apoptosis, inhibit the proliferation of mesenchymal stromal cells and may cause certain skeletal disorders (18). Low dose, short term doses may stimulate osteogenesis (18). This phenomenon may be beneficial in implant dentistry. Most studies use high long term doses of DX and thus may not be appropriate for single low dose DX study. The effects of DX on bone formation and especially on bone formation in grafted sites need elucidation.

One interesting side effect of DX is hiccups. Hiccups (singular: singultus, plural: singulata) are involuntary, spasms of the diaphragm (19). Hiccups lasting longer than 48 hours are considered pathological and may be indicative of a neurological disorder (19). Hiccups more commonly occur in patients with malignancies and infections, such as Covid-19, who are administered DX. (19). The low dosages of DX presented herein are unlikely to cause hiccups (20).

CASE EXAMPLES

A 67-year-old female presented for extraction and implant placement of an unrestorable mandibular first premolar (#21). The patient's medical history was unremarkable for dental implant treatment. The treatment risks and sequence were explained, and the patient accepted, and informed consent obtained. The site was locally anesthetized with 1.6cc articaine (Septocaine) and she orally rinsed with chlorhexidine. The unrestorable #21 was sectioned mesio-distally and the facial and lingual segments elevated out and the socket debrided. The site was then prepared in the usual fashion for immediate dental implant fixture placement. A 3.2X10mm Implant Direct implant was placed to 35ncm. Space between the implant fixture and the socket bone and above the implant platform was filled with an 80:20 mixture of an alloplast (Puros) and CaSO4. The socket was then covered with a collagen barrier (Ossix) and secured with 3-0 chromic suture (Gibson). 4mg DX was then infiltrated into the facial mucosa. The patient was instructed as to post-operative care. 24 hours later the patient was called. She reported that she had no pain or swelling. The patient returned at 7 days and reported no pain or swelling. After 4 months the implant was restored with a porcelain fused-to-noble alloy crown.

A 47 year old female requested treatment for painful and fractured mandibular left posterior teeth. After an options discussion and securing of informed consent the left mandible was infiltrated with 1.6cc articailne (Septiopcaine). 2000mg amoxicillin was orally administered preoperatively. The mandibylaur left premolare were carious and fractured and deemed unrestorable. A full thickness flap was raised. These were surgiucally extracted and thoroughly debrided. A 3.2X8 Implant Direct implant was placed in the fist moklar site and a 3.2X13 implant was immediately placed in the first premoalr socket. The area was covered with a 80:20 mix of alograft (Puros) and calcium sulfate. A collagen barroer was placed (Ossix). Primary closure was obtained with 3-0 chromic suture (Gibson). 4mg dexamethasone was infiltrated submucosally at the facial of the surgical site. The patient was prescribed amoxicillin 875mg BID and clorhexidene BID for 1 week. The next day the patient was called and asked to describe the pain she was having on a 1 out of 10 scale. She reported a 1. After 1 week the sutures were removed and the patient reported only slight soreness at that time. After 8 weeks healing was evaluated and found to be appropriate. After 4 months the implants were successfully restored with fixed cement retained crowns.

CONCLUSIONS

A single local 4mg submucosal infiltration of dexamethasone adjacent to the surgical site may be appropriate to minimize postoperative pain and swelling after dental implant surgery. Nonetheless, clinical trials are

needed to verify this and any effects on osseous healing. The single low 4mg dose used is very unlikely to induce severe side effects.

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