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EFFECT OF PERIOPERATIVE DEXAMETHASONE ON SURGICAL SITE HEALING IN PATIENTS WITH FACIAL FRACTURES

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ACADEMIC DISSERTATION

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

I Thorén H, Snäll J, Kormi E, Numminen L, Fäh R, Iizuka T, Lindqvist C, and Törnwall J. Does perioperative glucocorticosteroid treatment correlate with disturbance in surgical wound healing after treatment of facial fractures? A retrospective study. Journal of Oral Maxillofacial Surgery. 2009 Sep;67(9):1884-1888.

II Snäll J, Kormi E, Lindqvist C, Suominen AL, Mesimäki K, Törnwall J, and Thorén H. Impairment of wound healing after operative treatment of mandibular fractures, and the influence of dexamethasone. British Journal of Oral and Maxillofacial Surgery. 2013 Dec;51(8):808-812.

III Snäll J, Kormi E, Koivusalo AM, Lindqvist C, Suominen AL, Törnwall J, and Thorén H. Effects of perioperatively administered dexamethasone on surgical wound healing in patients undergoing surgery for zygomatic fracture: a prospective study. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology. 2014 Jun;117(6):685-689.

IV Snäll J, Kormi E, Lindqvist C, Suominen AL, Koivusalo AM, Törnwall J, and Thorén H. Pulp necrosis of teeth retained at the mandibular fracture site and the effect of dexamethasone on its occurrence. Dental Traumatology. In press, 2014 Oct 14.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
CRH	corticotropin-releasing hormone
DHEA	dehydroepiandrosterone
GC	glucocorticoid
DSWH	disturbance in surgical wound healing
DXE	dexamethasone
PN	pulp necrosis
ZC	zygomatic complex

ABSTRACT

Background and purpose

Short-term glucocorticoids (GCs) are frequently used in association with oral and maxillofacial surgery to prevent postoperative pain, edema, and nausea. However, the influence on tissue repair and the anti-inflammatory and immunosuppressive features of GCs may have an adverse impact on healing of the surgical site. The main aim of this study was to determine the occurrence of disturbance in surgical wound healing (DSWH) (Studies I–III) and pulp necrosis (PN) (Study IV) after surgical treatment of facial fractures and the influence of perioperative administration of GCs on these complications.

Patients

This study comprised four populations of patients (Studies I–IV) treated for facial fractures at the Department of Oral and Maxillofacial Diseases, Helsinki University Central Hospital, Helsinki, Finland. For Study I, the medical records of 280 consecutive patients who had undergone open reduction of different types of facial fractures or reconstruction of orbital wall fracture between January 1, 2003 and December 31, 2004 were retrieved from the database of the Department of Oral and Maxillofacial Diseases. The populations of Studies II and III were recruited at the department between June 1, 2006 and December 31, 2010. Study II comprised dentate patients who had simple mandibular fractures and were scheduled to undergo surgery through an intraoral approach (n=41). In Study III, patients with a simple zygomatic complex (ZC) fracture who were to undergo surgery through an extra- and/or intraoral approach (n=64) were recruited. The fourth population (n=24) (Study IV) was extracted from the population of patients with mandibular fractures recruited for Study II. Included in the analysis were those who had a fracture line in the tooth-bearing area anterior to the third molar.

Methods

In the retrospective study (Study I), the outcome variable was DSWH, which was established when any kind of aberrant wound healing and/or sign of infection in the surgical site occurred. The primary predictor variable was the perioperative use of GC.

Patients recruited for Studies II and III were randomly assigned to one of two groups. Patients in the study group received dexamethasone (DXE) (Oradexon®), whereas patients in the control group received no GC. Patients were followed up one day, two days, one week, one month, three months, and six months postoperatively. The main outcome variables were DSWH (Studies II–III) and PN of teeth in the area of mandibular fracture (Study IV). The primary predictor variable was the perioperative use of DXE.

Chi-square and Fisher's exact tests were used to study statistical significance of associations between outcome and categorized predictor variables. Wilcoxon two-sample test was used to evaluate differences in means of continuous variables.

Results

In patients operated on for ZC fractures (Study III), DSWH was significantly associated with perioperative use of DXE as well as with intraoral surgical approach. In patients operated on for different types of facial fractures (Study I), DSWH was associated significantly with intraoral surgical approach. In these patients, no significant association between DSWH and perioperative use of GCs was found; however, DSWH occurred more frequently in patients receiving GCs. In patients undergoing intraoral surgery for mandibular fractures (Study II), DSWH occurred more frequently in the DXE group. Also PN occurred more frequently in the DXE group (Study IV).

In patients with different types of facial fractures (Study I), all six patients who had received perioperative GCs and who ended up with DSWH had received the maximal number of GC doses used in the study population, i.e., a total of three 10-mg doses given at 8-hour intervals.

In patients with different types of facial fractures (Study I), mandibular fractures (Study II), and ZC fractures (Study III), the delay of DSWH was notably longer in the DXE groups. Particularly PN (Study IV) was observed much later in the DXE group.

Conclusions

Perioperative DXE cannot be recommended in association with surgery of ZC fractures. Moreover, GCs should be used with caution in association with surgery of other facial fractures as well, particularly when the intraoral approach is used. Patients who have teeth retained in the mandibular fracture line, in particular those who additionally receive perioperative GCs, should be referred to the general dentist for regular, long-term follow-up so that endodontic treatment can be initiated immediately when needed.

1. INTRODUCTION

Due to their anti-inflammatory effects, glucocorticoids (GCs) are widely used in association with surgery in order to decrease tissue reactions that cause discomfort postoperatively. GCs have been shown to successfully reduce swelling after various types of surgical procedures (Daull, Paterson et al. 2013, Tuncel, Turan et al. 2013). In association with oral and maxillofacial surgery in particular, GCs reduce both swelling (Dan, Thygesen et al. 2010) and pain (Dan, Thygesen et al. 2010, Markiewicz, Brady et al. 2008). GCs also reduce nausea caused by general anesthesia (Doksrod, Sagen et al. 2012, Bisgaard, Klarskov et al. 2003).

When GCs are applied perioperatively for the above-mentioned reasons, the duration of medication is short-lived, but the doses are usually high. Potential complications of high-dose application of GCs are avascular necrosis (Hussain, Young 2007, Chan, Chan et al. 2006, Wong, Poon et al. 2005), psychosis (Natkunarajah, Goolamali et al. 2011, Ularntinon, Tzuang et al. 2010, Fleming, Flood 2005, Galen, Beck et al. 1997), gastrointestinal ulcer (Olsen, Christensen et al. 2010, O'Neil, Chwals et al. 1992), and even gastrointestinal perforation and bleeding (Fadul, Lemann et al. 1988). In addition, GCs impair the immune defense by various mechanisms (Schimmer, Parker 2006), and short-term, high-dose usage might have such adverse effects as infections and impairment of surgical site healing.

In animals, delayed healing of the surgical wound has been shown to occur after short-term use of GCs (Li, Wang et al. 2012, Durmus, Karaaslan et al. 2003, Wicke, Halliday et al. 2000). Human studies, on the other hand, reveal contradictory results. The use of GCs in association with thyroid surgery, laparoscopic cholecystectomy, laparotomy for endometrial cancer, or cardiac surgery has not caused any problems in surgical wound healing (Bolac, Wallace et al. 2013, Doksrod, Sagen et al. 2012, Dieleman, Nierich et al. 2012, Bisgaard, Klarskov et al. 2003, Polat, Nayci et al. 2002). Studies that have focused on surgical procedures in the oral cavity have also yielded contradictory results. In some studies, GCs caused no adverse effects on oral surgical wound healing (Bortoluzzi, Capella et al. 2013, Antunes, Avelar et al. 2011, Dan, Thygesen et al. 2010, Markiewicz, Brady et al. 2008), whereas other authors have observed higher rates of fistulas, alveolar osteites, and other manifestations of infection (Dan, Thygesen et al. 2010, Senders, Di Mauro et al. 1999).

There is a significant lack of investigations focusing on the benefits and drawbacks of GC use in association with surgical treatment of facial fractures. To date, we have found only one randomized study on this topic (Flood, McManners et al. 1999). The authors of that study

observed significant benefits of short-term, high-dose methylprednisolone on tissue recovery after surgery of traumatized orbits. No complications related to GC were reported; however, the patients were followed up for 72 hours only, a time-span that is far too short to identify GC-related problems. Considering the fact that GCs are widely used in association with craniofacial surgery (Assimes, Lessard 1999), an obvious need for investigations about the drawbacks of GC use in this context exists.

2. REVIEW OF THE LITERATURE

2.1 Facial fractures

Facial fractures are frequent in traumatized patients, and, vice versa, patients with facial injuries frequently have injuries in other parts of the body (Thorén, Snäll et al. 2010, Follmar, Debruijn et al. 2007). Assault is the main mechanism of facial fractures in Finland (Thorén, Snäll et al. 2010), parallel findings also arising from other Western countries (Allareddy, Allareddy et al. 2011, van den Bergh, van Es et al. 2011). Other common trauma mechanisms are traffic accidents (van Hout, Van Cann et al. 2012, Naveen Shankar, Naveen Shankar et al. 2011, Kontio, Suuronen et al. 2005, Gassner, Tuli et al. 2003), falls (Singh, Malkunje et al. 2012), bicycle accidents (Boffano, Roccia et al. 2013), and sports-related accidents (van Hout, Van Cann et al. 2012, Zix, Schaller et al. 2011). Men are involved more often than women, especially when it comes to assault-related injuries (van den Bergh, van Es et al. 2011, Thorén, Snäll et al. 2010).

A nasal bone fracture is the single most common facial fracture, other common injuries being mandibular fractures and fractures of the zygomatico-orbital complex (Kyrgidis, Koloutsos et al. 2013, van Hout, Van Cann et al. 2012, Naveen Shankar, Naveen Shankar et al. 2011, Thorén, Snäll et al. 2010). Facial fractures are also frequently multiple and severe (Figure 1) (Thorén, Snäll et al. 2010).

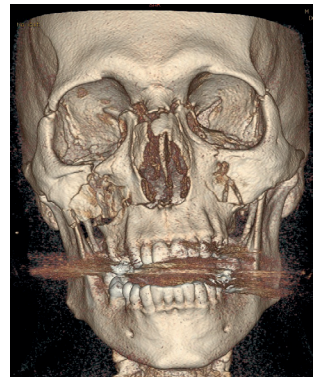

Figure 1. Severe midfacial fracture as a result of an assault. The three-dimensional computer tomography reconstruction shows combination of Le Fort I–III type fractures. The upper fracture lines extend to the base of the skull. The right bony orbit is widely fragmented.

Facial fractures that cause esthetic and/or functional disturbances need to be corrected surgically. The fracture site is exposed, after which the fractured fragments are adjusted to the correct position and fixed with plates and screws. The injury itself (Figure 2) and surgical intervention cause swelling and pain, indicating the use of anti-inflammatory drugs during and after surgery. On the other hand, delayed healing of the wound and infections

at the surgical site remain the main complications of facial fracture surgery (Ellis 2013, Salentijn, van den Bergh et al. 2013). Therefore, anti-inflammatory drugs, which may impair wound healing and cause surgical infections, should be used with caution.

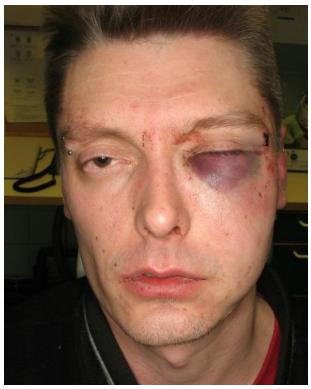

Figure 2. Recent fracture of the left zygomatic bone causing significant swelling of the lower lid and cheek

2.2 Healing of soft tissues

Repair of soft tissues can be divided into three main phases: inflammation, proliferation, and maturation. These complex processes occur partly contemporaneously. The inflammatory phase includes hemostasis and inflammation. Proliferation includes remodeling and granulation. Maturation, which may last from months to years, includes re-epithelization and tissue formation.

Surgical wounds are mainly clean wounds without tissue defects. Therefore, the sides of the wounds can be settled against each other, leading to *healing by primary union*. In more complex wounds, the healing process is slower due to tissue loss, and the healing process requires more connective tissue and scar formation; this form of healing is called *healing by secondary union.* This also takes place if healing by primary union fails. The complex process of healing is regulated by proteases, cytokines, chemokines, peptides, and genetic characteristics (Schreml, Szeimies et al. 2010).

Clinically, the most important cause of delay in wound healing is infection. Other important factors that influence tissue repair are nutrition, perfusion, mechanical variables (such as degree of local pressure), possible foreign bodies in the wound, and several diseases and medications (Kumar, Abbas et al. 2012)

2.3 Basic mechanisms of fracture healing

Bone healing follows the mechanisms of soft tissue repair and is regulated by similar complex mechanisms (Arvidson, Abdallah et al. 2011, Phillips 2005, Einhorn 1998). Fracture healing is divided into two phases; primary and secondary. In primary healing, osteoclasts migrate across the fracture site, resulting in high bone stability (Phillips 2005). In secondary healing, a mass of non-calcified soft tissue callus is first created, followed by cartilage synthesis (Kumar, Abbas et al. 2012, Phillips 2005). Ossification of the callus optimally results in the original size, shape, and integrity of the bone.

From a clinical point of view, displaced and comminuted fractures as well as inadequate fracture immobilization are significant factors that increase the risk for incomplete healing (Kumar, Abbas et al. 2012).

2.4 Glucocorticoids

GCs (i.e., in humans, cortisol and its biologically active synthetic derivatives) are a group of steroid hormones that affect the metabolism of carbohydrates, fats, and proteins, in addition to many other effects.

Cortisol is synthesized and released from the adrenal cortex following activation of the hypothalamic-pituitary-adrenal axis, which is induced by stress. The hypothalamic corticotropin-releasing hormone (CRH) regulates secretion of adrenocorticotropic hormone (ACTH) in the pituitary. ACTH stimulates the adrenal cortex to secrete GCs, mineralocorticoids, and dehydroepiandrosterone (DHEA). GCs are bound to plasma proteins and transported to tissues to interact with specific receptor proteins. GC receptors are found in nearly every cell of the human. Recent studies have indicated that GCs act through several receptor subtypes instead of a single GC receptor (Oakley, Cidlowski 2011, Bray, Cotton 2003). Their contribution to the sensitivity and specificity of the GC response is currently of interest (Oakley, Cidlowski 2011).

2.4.1 Synthetic glucocorticoids in medicine

The immunosuppressive and anti-inflammatory actions of GCs are well known. Their effects are mediated by multiple mechanisms, and the network of the cascades is extensive. Although the immunosuppressive effects of GCs in general are widely known, the precise mechanisms remain unclear (Oakley, Cidlowski 2011, Didonato, Saatcioglu et al. 1996, Marx 1995). Suppression of inflammation is caused by a decreased release of vasoactive and chemoattractive factors, diminished secretion of proteolytic and lipolytic enzymes, decreased fibrosis, a lower number of circulating lymphocytes, and reduced extravasation of leucocytes to the site of injury (Schimmer, Parker 2006). Due to these effects, GCs are used to treat several autoimmune diseases, acute and chronic inflammatory diseases, organ transplant rejection, and malignancies of the lymphoid system (Rhen, Cidlowski 2005). GCs can also be used to substitute deficiencies in secretion of human cortisol.

GCs have several side-effects that need to be considered. They may depress the function of the adrenal cortex, leading to a decreased secretion of cortisol. Other significant side-effects are immunodeficiency, osteoporosis, changes in glucose and fat metabolism, and atrophy of skin and muscles.

Table 1. Relative potencies and equivalent doses of glucocorticoids.

Glucocorticoid	Anti-inflammatory potency	Relative mineralo-corticoid activity	Relative glucocorticoid activity	Biological half-life*	Equivalent dose in oral or intravenous administration (mg)
Cortisol (Hydrocortisone)	1	1	1	short	20
Cortisone	0.8	0.8	0.8	short	25
Prednisone	4	0.8	4	intermediate	5
Prednisolone	4	0.8	4	intermediate	5
Methyl-prednisolone	5	0.5	5	intermediate	4
Triamcinolone	5	0	5	intermediate	4
Betamethasone	25	0	20–30	long	0.75
Dexamethasone	25	0	20–30	long	0.75

*short: 8–12 hours, intermediate: 12–36 hours, long: 36–54 hours

Modified from Goodman & Gilman´s The Pharmacologian Basis of Therapeutics 11th edition, 2005. Table 59-2 p. 1594.

Various synthetic GCs are available for several medical applications. Synthetic GCs differ from each other with regard to pharmacokinetics and pharmacodynamics (Table 1). Therefore, GCs can be chosen based on the desired effects.

2.4.2 Short-term glucocorticoids

The short-term use of GCs differs from long-term use, the benefits and side-effects being somewhat different. In short-term use, the dosages are usually higher and a wider potency is preferred than in long-term use.

2.4.2.1 Benefits

To diminish postoperative nausea and vomiting, anesthesiologists favor dexamethasone (DXE) (Diakos, Gallos et al. 2011, Karanicolas, Smith et al. 2008, Bolton, Myles et al. 2006, Bisgaard, Klarskov et al. 2003). DXE is also effective in reducing pain in general (De Oliveira, Almeida et al. 2011, Diakos, Gallos et al. 2011, Steward, Grisel et al. 2011, Afman, Welge et al. 2006, Bisgaard, Klarskov et al. 2003) and especially migraine headache (Colman, Friedman et al. 2008). In cardiac surgery patients, recovery improved significantly when DXE was used (Murphy, Sherwani et al. 2011).

GCs have been proven to reduce edema after various types of interventions such as ophthalmologic interventions (Daull, Paterson et al. 2013, Grover, Li et al. 2008), neurosurgery (Kotsarini, Griffiths et al. 2010), rhinological procedures (Tuncel, Turan et al. 2013, Hatef, Ellsworth et al. 2011), and surgery of fractured orbits (Flood, McManners et al. 1999).

GCs have been studied as adjunct therapy in patients with serious infections, but a consistent view of their benefits has yet to emerge (De Pascale, Bello et al. 2011, Moran, Graham et al. 2010, Agarwal, Nath et al. 2007). GCs appear to be beneficial when low doses are used, whereas adverse effects seem to increase when doses are increased (Minneci, Deans et al. 2004).

2.4.2.2 Drawbacks

GCs occasionally have serious side-effects, particularly when high doses are used. The risk for adrenal suppression in association with short-term use continues for several months after the medication ceases (Henzen, Suter et al. 2000). Short-term GCs increase the risk for avascular osteonecrosis (Hussain, Young 2007, Chan, Chan et al. 2006, Wong, Poon et al. 2005). Even though the cases are rare, the literature reports GC-induced psychosis, especially in connection with high doses (Natkunarajah, Goolamali et al. 2011, Ularntinon, Tzuang et al. 2010, Fleming, Flood 2005, Galen, Beck et al. 1997). GCs have also been shown to increase the incidence of peptic ulcers and gastrointestinal bleeding (O'Neil, Chwals et al. 1992), and high-dose GC use is associated with a greater increase in mortality following peptic ulcer bleeding (Olsen, Christensen et al. 2010). In addition, short-term GCs have various adverse effects on tissue healing.

2.4.3 Effects of short-term glucocorticoids on tissue healing

The altered cellular function caused by GCs is transmitted through induction of gene transcription (Schimmer, Parker 2006). The GC receptor interacts with proteins, which control proinflammatory gene expression (Stocklin, Wissler et al. 1996), inducing diminished healing (Sanchis, Alba et al. 2012). GCs can also induce apoptosis (Schlossmacher, Platt et al. 2013, Zhu, Zhao et al. 2013, Yang, Lou et al. 2011). In addition to direct cellular influences, there are several other GC-related mechanisms that should be taken into consideration in surgical wound healing.

2.4.3.1 Altered functions in periphery

GCs alter the functions and concentrations of cells critical in inflammatory response and tissue repair. They affect the concentration of blood cells by decreasing the numbers of circulating lymphocytes, eosinophils, basophils, and monocytes and increasing the numbers of circulating polymorphonuclear granulocytes and stab cells (Derendorf, Hochhaus et al. 1993). GCs also increase blood glucose levels (Doksrod, Sagen et al. 2012, Nazar, Lacassie et al. 2009, Derendorf, Hochhaus et al. 1993) and inhibit the proliferation of fibroblasts (Ramalingam, Hirai et al. 1997). Moreover, GCs decrease collagen synthesis and levels of growth factors in wounds (Wicke, Halliday et al. 2000).

GCs play a role in vascular tone and vascularization. GCs control vascular tone by suppressing vasodilatation in endothelial cells (Jun, Chen et al. 1999, Zingarelli, Caputi et al. 1994) and have an indirect effect on vascular tone by increasing vascular sensitivity to vasoconstrictors in vascular smooth muscle cells (Xiao, Huang et al. 2003). In addition, GCs inhibit the growth of blood vessels (Hasan, Tan et al. 2000, Folkman, Langer et al. 1983). Especially DXE has been shown to inhibit angiogenesis (Hori, Hu et al. 1996). Although the precise mechanisms remain unresolved, it has been established that GCs interact directly with GC receptors on vascular endothelial cells (Logie, Ali et al. 2010). Genetic variations of GC receptors also have a significant consequence in vasoconstriction (Kumsta, Entringer et al. 2008). Table 2 summarizes the influence of GCs on different cell types in the periphery.

The above-mentioned various effects of GCs on cells and molecules show that even short-term GCs have a significant potential to impair surgical site healing.

Table 2. Main effects of glucocorticoids on different cell types in inflammatory and immune responses according to literature.

Cell type	Influence of glucocorticoids	Mechanisms
Polymorphonuclear leucocytes	Increase of circulating cells	- increased release from the marrow - diminished rate of removal from circulation
Lymphocytes, eosinophils, basophils, and monocytes	Decrease of circulating cells	- redistribution of cells away from the periphery
Fibroblasts	Decrease of acting cells	- inhibition of proliferation - reduction of cell viability
Endothelial cells	Decrease of acting cells, vasoconstriction	- suppression of vasodilatation - effects on vasoconstrictors - inhibition of proliferation
Vascular smooth muscle cells	Vasoconstriction	- increase of vascular sensitivity to vasoconstrictors

2.4.3.2 Short-term glucocorticoids and surgical site recovery

Several animal studies have shown that use of short-term GCs in association with surgery predisposes to imperfect wound healing (Li, Wang et al. 2012, Durmus, Karaaslan et al. 2003, Wicke, Halliday et al. 2000). Durmus et al. (2003) showed that a single dose of DXE 1 mg/kg administered intraperitoneally in rats had a deleterious effect on wound healing (Durmus, Karaaslan et al. 2003). Also collagenization, epithelization, and fibroblast contents were significantly lower in rats receiving DXE than in those receiving physiological saline. Human studies, on the other hand, have yielded contradictory results about the adverse effects of GCs on surgical wound healing.

In a study of thyroid surgery patients (Doksrod, Sagen et al. 2012), DXE showed no association with postoperative disturbance in wound healing. Another study found no evidence of an increased risk of surgical site infections after gynecological surgery when a single dose of DXE (4–12 mg) had been used (Bolac, Wallace et al. 2013, Eberhart, Holdorf et al. 2011). Also after uvulopalatopharyngoplasty, healing of the surgical wound was uneventful despite the use of GC (Williams, Strome et al. 1999). By contrast, a study focusing on non-emergency trauma patients revealed an increased risk of infections after surgery in patients who received DXE perioperatively (Percival, Riddell et al. 2010). The authors stated that DXE increases the risk of postoperative infection, particularly during the first postoperative month. A recent study of cardiac pediatric patients showed an association between duration of short-term corticosteroid exposure and postoperative infections (Mastropietro, Barrett et al. 2013). Several reasons exist for the discrepancies in results: among others, the types, dosages, and durations of GCs as well as the types of surgical procedures vary significantly between the studies.

2.5 Glucocorticoids in oral and maxillofacial surgery

The interest in the use of GCs in association with oral and maxillofacial surgery was awakened in the 1950s (Ross, White 1958, Stewart 1956). Since then, the usefulness of GCs has been investigated particularly in association with third molar surgery, and several studies have demonstrated benefits of GCs on recovery (Dan, Thygesen et al. 2010, Markiewicz, Brady et al. 2008). Local injection has shown benefits similar to those of systemic administration (Warraich, Faisal et al. 2013, Antunes, Avelar et al. 2011). According to a questionnaire filled out by oral and maxillofacial surgeons, perioperative GCs are favored especially because of their ability to reduce postoperative edema (Assimes, Lessard 1999), an effect that has been shown in several studies (Dan, Thygesen et al. 2010, Markiewicz, Brady et al. 2008, Flood, McManners et al. 1999). GCs also reduce pain after surgical procedures in the oral cavity in general (Dan, Thygesen et al. 2010) and have beneficial effects on neurosensory recovery after orthognathic surgery in particular (Al-Bishri, Rosenquist et al. 2004, Seo, Tanaka et al. 2004).

The association between GC and disturbance in surgical site healing after oral surgery was discussed already in the late 1960s by Hooley et al. (1969). The investigators clarified the benefits and drawbacks of betamethasone in third molar surgery. Patients were randomized to receive either placebo or a total dose of 14.4 mg of betamethasone, which was administered over three days, beginning one day before surgery. A double-blind method was used. Forty-seven patients were included in the study, and a total of 94 third molars were extracted. Follow-up revealed alveolar osteitis in two patients, both of whom had received betamethasone. Since this study by Hooley et al., numerous randomized studies on the benefits of perioperative GC application in association with third molar surgery have been published, but very few report any surgical site complications. However, patients included in third molar studies have usually been followed up for only about one week (Bortoluzzi, Capella et al. 2013, Mehra, Reebye et al. 2013, Antunes, Avelar et al. 2011, Dan, Thygesen et al. 2010, Markiewicz, Brady et al. 2008). Since surgical site complications may occur several weeks after surgery (Monaco, Tavernese et al. 2009), a follow-up of one week is not sufficient.

Some studies report that no complications occur in cleft palate surgery despite the use of GC (Bateman, Conejero et al. 2006, Senders, Emery et al. 1996). Another study has shown, however, a higher rate of postoperative palatal fistulas in patients receiving DXE (9%) than in those receiving placebo (4%) (Senders, Di Mauro et al. 1999). Although this finding was not statistically significant, it is notable.

A prospective randomized study of 33 patients who had undergone orthognathic surgery observed no complications related to perioperative GC administration (Weber, Griffin 1994). Another study focusing mainly on the benefits of GCs reported no complications in 39 patients undergoing orthognathic surgery, however, the follow-up was only 72 hours (Schaberg, Stuller et al. 1984). A third study that focused on 36 pediatric patients undergoing orthognathic surgery showed no surgical wound complications related to GC (Munro, Boyd et al. 1986), but two patients who had received GCs were reported to have postoperative bleeding.

Clinical trials focusing on the use of GCs in facial trauma patients are scarce. Flood et al. published in 1999 a prospective, double-blind, randomized trial of 20 patients operated on for orbital blow-out fractures (Flood, McManners et al. 1999). The authors observed significant benefits of perioperatively applied GC. Those 11 patients who received 250 mg of methyprednisolone given four times at 6-hour intervals (i.e., a total dose of 1000 mg of methylprednisolone, which is equivalent to 190 mg of DXE) had a significantly increased interpalpebral width compared with those 9 patients who received placebo. Despite the high dosage, no complications appeared; however, the follow-up of patients was only 72 hours.

3. AIMS OF THE STUDY

The occurrence of disturbance in surgical wound healing (DSWH) and pulp necrosis (PN) after surgical treatment of facial fractures and the influence of perioperative glucocorticoid (GC) administration on these complications were evaluated.

Specific aims were as follows:

1. To clarify the types of GC regimens used in association with operative treatment of different facial fractures and the influence of GC on the occurrence of DSWH (Study I).

2. To determine the occurrence of DSWH after operative treatment of mandibular fracture and the influence of dexamethasone (DXE) (Study II).

3. To determine the occurrence of DSWH after operative treatment of zygomatic complex (ZC) fracture and the influence of DXE (Study III).

4. To evaluate the occurrence of PN of teeth in the fracture area after operative treatment of mandibular fracture and the influence of DXE (Study IV).

4. PATIENTS AND METHODS

4.1 Study populations

This study comprised four populations of patients (Studies I–IV) treated for facial fractures at the Department of Oral and Maxillofacial Diseases, Helsinki University Central Hospital, Helsinki, Finland.

For the first study (I), the medical records of 280 consecutive patients who had undergone open reduction of different types of facial fractures (with or without osteosynthesis) or reconstruction of orbital wall fracture between January 1, 2003 and December 31, 2004 were retrieved from the database of the Department of Oral and Maxillofacial Diseases.

The populations of Studies II–IV were recruited at the department between June 1, 2006 and December 31, 2010. Patients included were at least 18 years old. Patients with infected fractures were excluded, as were patients with a history of liver dysfunction, kidney dysfunction, peptic ulcer, psychosis due to GC use, pregnancy, breastfeeding, or allergy to any constituent of the DXE preparation.

Recruited patients for Study II (n=41) comprised dentate patients who had one or 2 simple, non-comminuted, and non-complicated mandibular fractures and who were to undergo open reduction and osteosynthesis through an intraoral approach with the aid of 2.0 mm titanium miniplates according to the technique described by Champy and Lodde (1976) (Figures 3–4). The fracture types included were classified as follows: one single fracture in the angle, one single fracture in the body, one single fracture in the symphysis/parasymphysis area, or a double mandibular fracture (i.e., angle + body, angle + symphyseal/parasymphyseal fracture).

Recruited patients for Study III (n=64) comprised patients who had sustained a simple, non-comminuted ZC fracture (i.e. tripoid fracture) and were to undergo open reduction and fixation with the aid of one or more titanium miniplates through an extraoral and/or intraoral approach. Typical surgical access to the fronto-zygomatic suture through an upper blepharoplasty incision is shown in Figure 5 (page 26). Patients with any other facial fracture requiring surgery were excluded.

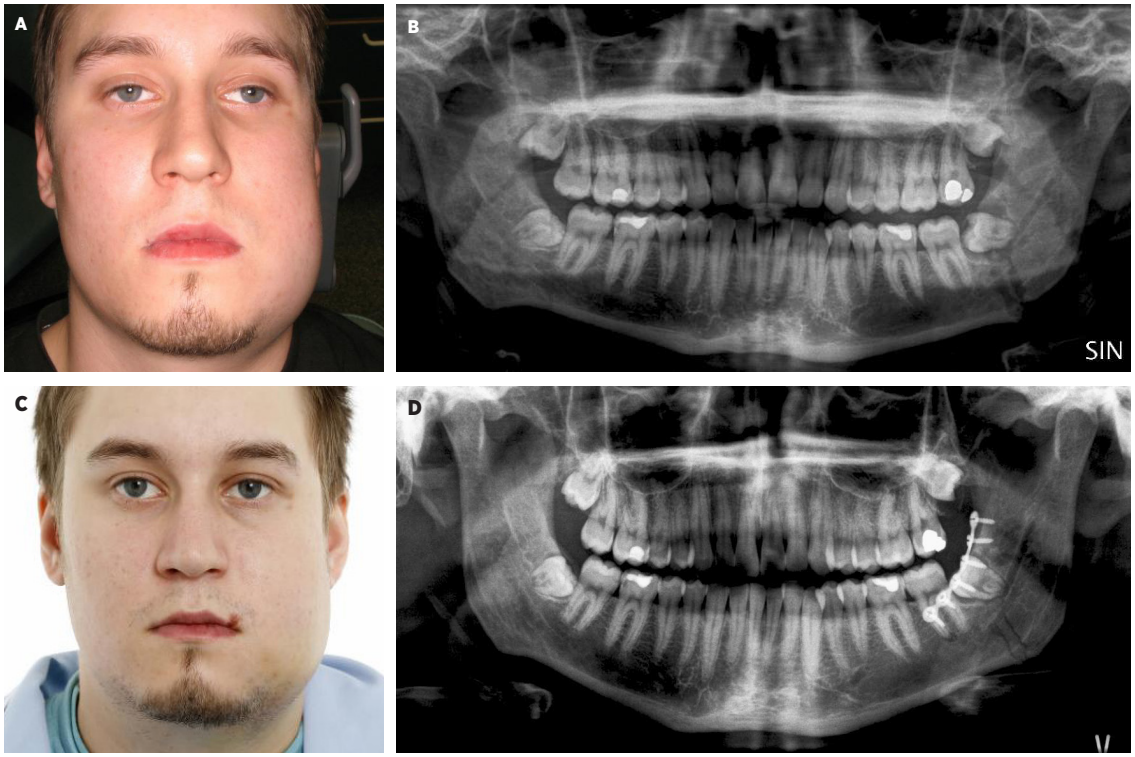

Figure 3. Left mandibular angle fracture treated with one miniplate according to the technique described by Champy and Lodde (1976). A: Preoperative extraoral swelling at the fracture site. B: Preoperative radiological view of the angle fracture. C: Extraoral swelling on the second postoperative day. D: Postoperative radiological view after the repositioning and osteosynthesis of the fracture.

The fourth patient population (Study IV, n=24) was extracted from those patients with mandibular fractures who had been recruited for Study II. Patients with at least one fracture line in the tooth-bearing area anterior to the third molar were included. Excluded from the final analysis were patients with teeth in the fractured area that either showed signs of chronic periodontal or periapical pathologies on pre-operative radiographs, had undergone endodontic treatment before the injury, or were fractured in association with the injury.

4.2 Outcome variables

The main outcome variables were DSWH (Studies I–III) and PN of teeth in the area of mandibular fracture (Study IV). DSWH was established when any kind of aberrant wound healing and/or sign of infection in the surgical site occurred. PN was confirmed in association with the initiation of endodontic treatment.

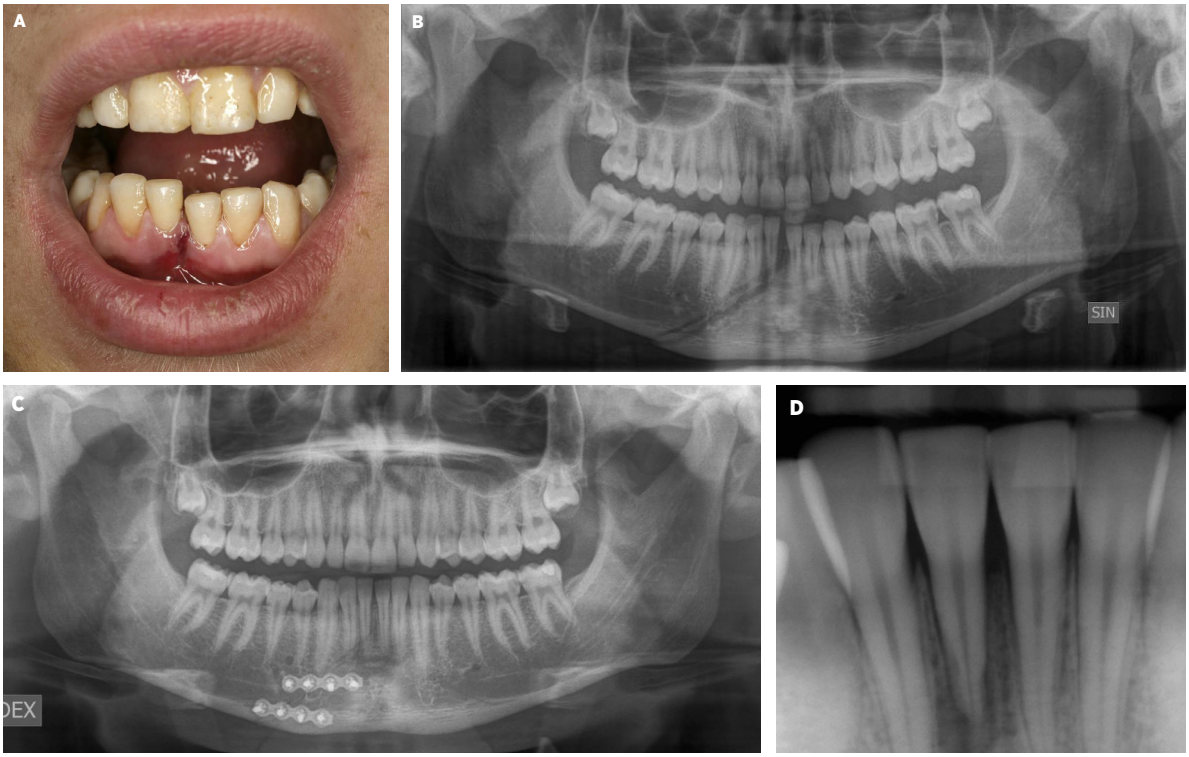

Figure 4. Fracture of the right parasymphysis area treated with two miniplates according to the technique described by Champy and Lodde (1976). A. Intraoral fractures site showing displacement. B. Preoperative radiological view of the mandibula. C. Postoperative radiological view. D. A periapical radiograph showing external resorption of d 41 three months after surgery.

4.3 Predictor variables

The primary predictor variable was the perioperative use of GC. Other predictor variables included in the analyses were gender and age (Studies I–IV), smoking habit (i.e., smoker or non-smoker) (Studies II and IV), site of fracture (Studies II and IV), type of fracture (Study I), treatment delay (i.e., time delay between accident and operative treatment) (Studies I–III), qualification of the surgeon (i.e., consultant or registrar) (Study I), surgical approach to the fracture line (i.e., intra- or extraoral), (Studies I and III), and duration of surgery (Studies II and III).

In Study I, the predictor variable "fracture type" was determined for each patient from 1 of the following 5 groups: 1) exclusively mandibular fracture (one or more), 2) exclusively zygomatico-orbital fracture (i.e., tripoid zygomatic fracture or isolated zygomatic arch fracture), 3) exclusively orbital blow-out fracture (i.e., isolated orbital floor or medial wall fracture), 4) severe midfacial fracture (i.e., Le Fort I to III, naso-orbito-ethmoidal or multiple midfacial fracture), and 5) combined mandibular-midfacial or panfacial fracture.

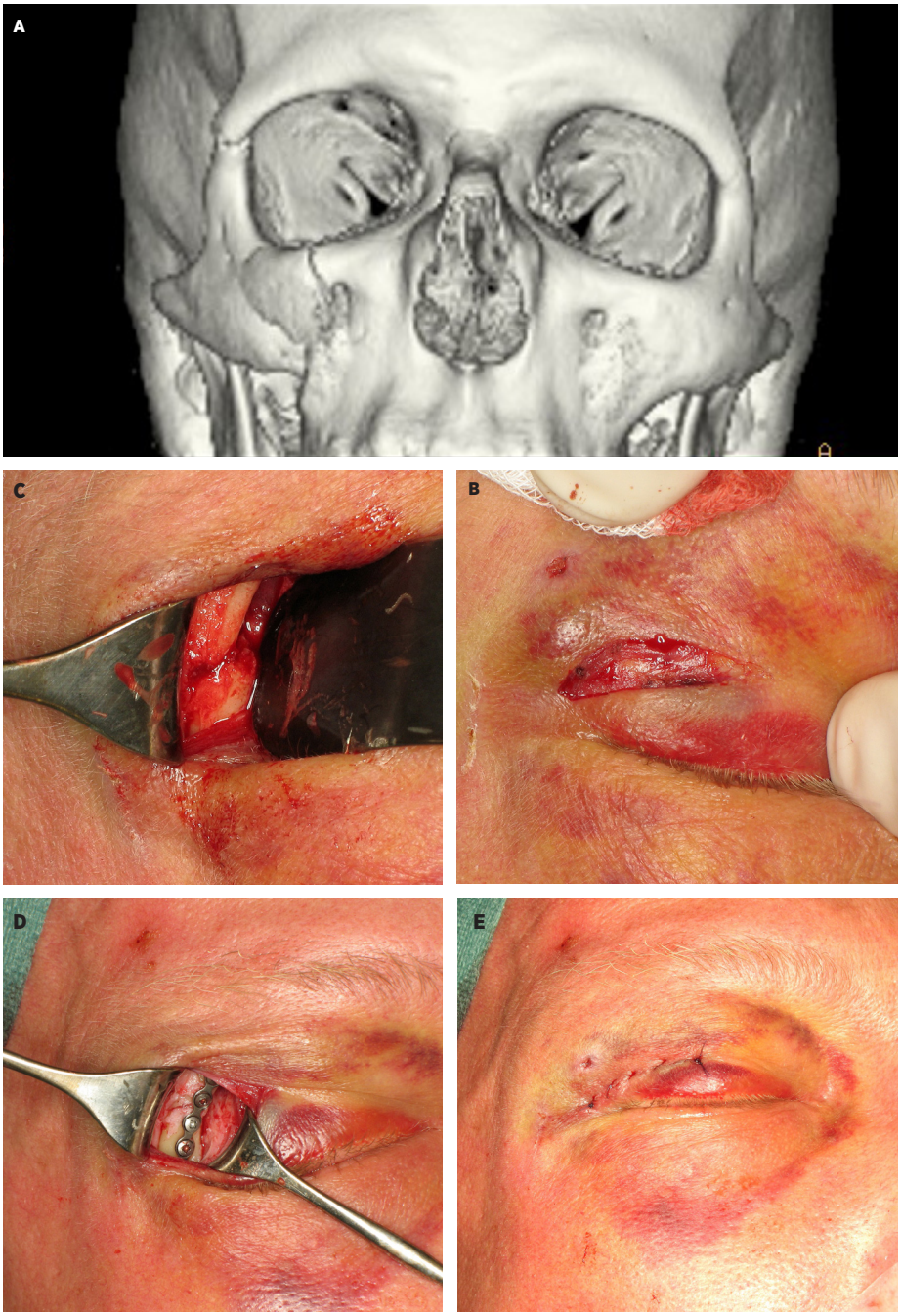

Figure 5. Surgical treatment of a right-sided zygomatic fracture through an upper blepharoplasty incision. A. Preoperative radiological view. B. Upper blepharoplasty incision. C. Fracture line at the frontozygomatic suture. D. Fracture stabilized with one (KLS Martin 1.5 mm) miniplate. E. Immediate postoperative view.

4.4 Dexamethasone regimens (Studies II and III)

For each facial fracture type, patients were randomly assigned to one of two groups. The patients in the study group received DXE (Oradexon®), whereas the patients in the control group received no GC.

The patients in the study group received either a single dose of 10 mg of DXE intravenously during anesthesia induction (Study III) or an additional 10 mg intramuscularly every 8 hours over 16 hours, to a total dose of 30 mg of DXE (Studies II, III). All patients received antibiotics until the seventh to tenth postoperative day, starting with three 1.5-g doses of cefuroxime intravenously at the ward during the first 24 hours postoperatively, followed by three daily doses of 500 mg of cephalexin orally. Patients with allergies received four daily doses of clindamycin via corresponding routes.

4.5 Clinical and radiological follow-up regimens (Studies II–IV)

Patients in Studies II–IV were followed-up clinically one day, two days, one week, one month, three months, and six months postoperatively. Patients received a longer follow-up for surgical reasons when needed. However, a postoperative follow-up period of 30 days (Studies II and III) or 3 months (Study IV) was required for a patient to be included in the final analysis.

In patients with mandibular fracture (Studies II and IV), radiological investigation with panoramic imaging was done immediately and at one month, three months, and six months postoperatively.

4.6 Evaluation of mandibular teeth in the fractured area (Study IV)

At each follow-up appointment, patients in Study IV were asked about dental symptoms. A routine clinical investigation of the teeth in the area of the mandibular fracture was performed, including an investigation with an electrical pulp tester. In addition to the routine investigations with panoramic imaging, teeth in the fractured areas were followed up with periapical x-rays (Figure 4D). Whenever there was a suspicion of a need for endodontic treatment, the patient was referred to an endodontist for further evaluation and therapy as required.

4.7 Statistics

Chi-square (Studies I–III) and Fisher's exact (Study III) tests were used to evaluate significance of associations between outcome (DSWH in Studies I–III and PN in Study IV) and categorized predictor variables. Wilcoxon two-sample test was used to evaluate differences in means of continuous variables, including age, delay in treatment (days) (Study II), duration of operation (minutes) according to the occurrence of DSWH (Study II), delay in DSWH (days) (Studies I–III), and delay in PN (days) (Study IV).

4.8 Ethical considerations

The protocol of Study I was approved by the Internal Review Board of the Division of Musculoskeletal Surgery, Helsinki University Central Hospital, Finland. The protocols of Studies II–IV were approved by the Research Ethics Board of the Department of Surgery and the Internal Review Board of the Division of Musculoskeletal Surgery, Helsinki University Central Hospital, Finland. All patients recruited for Studies II–IV signed a written consent. In addition, a signed written consent to publish facial photographs was obtained from those patients whose facial images are presented here.

5. RESULTS

5.1 Glucocorticoid regimens used in association with operative treatment of different types of facial fractures and influence of glucocorticoids on the occurrence of disturbance in surgical wound healing (Study I)

Descriptive statistics of the 280 patients are shown in Table 3. GCs had been administered to 100 patients (35.7%). All patients had received antibiotic treatment, which was initiated on admission and continued for 7 to 10 days postoperatively.

As shown in Table 4, GC regimens varied significantly. The most frequently used GC was DXE (accounting for 82% of those receiving GCs), followed by methylprednisone (14%) and hydrocortisone (4%). The total number of doses varied from 1 to 3, and the total doses, as equivalent to DXE, varied from 3.8 to 30 mg. The total length of medication varied from 1 to 24 hours. The single dose or first dose was administered intravenously during the operation to all patients. Postoperative doses were given either intravenously or intramuscularly. The most common regimen was DXE 10 mg every 8 hours over 16 hours (total dose 30 mg).

Table 3. Descriptive statistics of 280 patients with different types of facial fractures (Study I).

Age	**Years**
Range	11.2–72.6
Mean	35.9
Gender	**No. of patients**
Female	57
Male	223
Glucocorticoid	
yes	100
no	180
Fracture type	
Exclusively mandibular (one or more)	122
Zygomatico-orbital	102
Exclusively orbital blow-out	20
Severe midfacial	26
Combined mandibular-midfacial or panfacial	10
Surgical approach	
Exclusively extraoral	129
Intraoral or combined extra-intraoral	151

Table 4. Glucocorticoid regimens and occurrence of DSWH in 100 patients receiving perioperative glucocorticoids (Study I).

	Dose	Frequency	Total dose (mg)	Total dose equivalent to dexamethasone (mg)	No. of patients	No. of patients with DSWH
Dexamethasone	5 mg	Single dose	5	5	1	0
Dexamethasone	10 mg	Single dose	10	10	20	0
Dexamethasone	5 mg	Every 8 h	15	15	1	0
Dexamethasone	10 mg	Every 8 h	20	20	3	0
Dexamethasone	10 mg	Every 12 h	20	20	2	0
Dexamethasone	10 mg	Every 8 h	30	30	53	6
Dexamethasone	10 mg	Every 12 h	30	30	2	0
Hydrocortisone	100 mg	Single dose	100	3.8	2	0
Hydrocortisone	250 mg	Single dose	250	9.4	2	0
Methylprednisone	20 mg	Single dose	20	3.8	1	0
Methylprednisone	40 mg	Single dose	40	7.6	8	0
Methylprednisone	40 mg	Every 8 h	80	15.2	3	0
Methylprednisone	40 mg	Every 12 h	80	15.2	1	0
Methylprednisone	40 mg	Every 8 h	120	22.8	1	0

DSWH: Disturbance in surgical wound healing

DSWH was observed in 11 patients (3.9%) on average 47 (range 7–161) days after surgery. DSWH occurred more often in patients who received GCs (6.0%) than in those who did not (2.8%), but the difference was not statistically significant. The occurrence of DSWH in patients who received DXE was dose-dependent: all patients with DSWH had received 30 mg of DXE over 16 hours, i.e., the overall largest DXE dose that had been used (Table 4). DSWH was established on average 52 days after surgery in patients receiving DXE, the corresponding delay in patients not receiving DXE being 42 days (p=ns). No significant correlation existed between DSWH and age, gender, treatment delay, fracture type, or qualification of the surgeon. The only significant predictor of DSWH was intraoral surgical approach ($p < 0.001$)

5.2 Occurrence of disturbance in surgical wound healing after operative treatment of mandibular fracture and influence of dexamethasone (Study II)

A total of 49 patients fulfilled the inclusion criteria for Study II. Of these, 4 refused to participate. Of the remaining 45 patients, 4 were excluded: one because he attended no

follow-up appointments, one because he required an additional operation as the reduction of the fracture was unsatisfactory, and 2 because they failed to complete all doses. Forty-one patients were therefore followed up for at least one month. Descriptive statistics of the 41 patients are shown in Table 5.

Table 6 shows the association between DSWH and predictors. DSWH was observed in 13 patients (31.7%) on average 31 (range 2–93) days after surgery. A typical impairment of wound healing requiring plate removal is shown in Figure 6. DSWH occurred more often in patients who received GCs (35.0%) than in those who did not (28.6%), but the difference was not significant. In the DXE group, DSWH was established on average 42 days after surgery, the corresponding delay in patients not receiving DXE being 34 days (p=ns). No significant correlation existed between DSWH and gender, smoking habit, time span from accident to surgery, fracture site, or duration of surgery. The only significant predictor of DSWH was age over 25 years (p=0.016).

Table 5. Descriptive statistics of 41 patients with mandibular fractures (Study II).

Age	**Years**	
range	18.1–50.9	
mean	28.1	
Gender	**No. of patients**	**% of 41 patients**
female	1	2.4
male	40	97.6
Dexamethasone		
yes	20	48.8
no	21	52.2
Smoker		
yes	27	65.9
no	14	34.1
Fracture localization		
angle	15	36.6
body	2	4.9
symphysis/ parasymphysis	12	29.3
angle + body	2	2.9
angle + symphysis/ parasymphysis	10	24.4
Treatment delay	**Days**	
range	0–5	
mean	2.1	
Follow-up	**Days**	
range	30–680	
mean	277	
Duration of surgery	**Minutes**	
range	23–129	
mean	53.9	

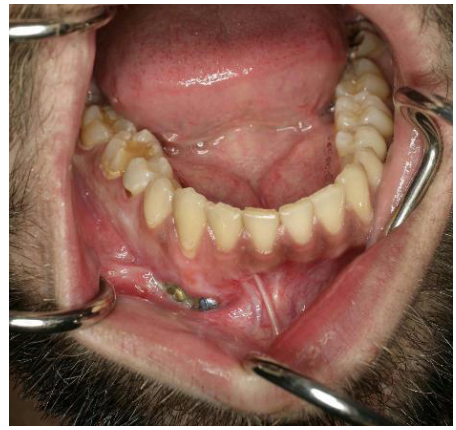

Figure 6. Disturbance in surgical wound healing at four months after surgery of a mandibular parasymphysis fracture just before plate removal. Screws and plate (Synthes 2.0) are uncovered and needed to be removed to obtain adequate wound healing. The patient did not receive perioperative glucocorticoids.

Table 6. Association between DSWH and predictor variables in 41 patients with mandibular fractures (Study II).

	DSWH present	% of n
Age group		
18–25 years	4	20
> 25 years	9	43
p=0.016		
Gender		
female (n = 1)	1	100
male (n = 40)	12	30.0
p=ns		
Dexamethasone		
yes (n = 20)	7	35.0
no (n = 21)	6	28.6
p=ns		
Smoker		
yes (n = 27)	7	25.9
no (n = 14)	6	42.9
p=ns		
Localization of DSWH		
angle (n = 27)	9	33.3
body (n = 4)	1	25.0
symphysis/ parasymphysis (n = 22) p=ns	3	13.6
Treatment delay (days)		
< 2 (n=18)	4	22.2
≥ 2 < 3 (n=15)	6	40.0
≥ 3 ≤ 5 (n=8)	3	37.5
p=ns		
DSWH present (days postoperatively)		
range	2–93	
mean	38.4	
median	33	

DSWH: Disturbance in surgical wound healing

Table 7. Descriptive statistics of 64 patients with zygomatic complex fractures (Study III).

Age	**Years**	
range	22.2–83.8	
mean	42.6	
Gender	**No. of patients**	**% of n**
female	18	28.1
male	46	71.9
Dexamethasone		
yes	33	51.6
no	31	48.4
Treatment delay	**Days**	
range	1–18	
mean	5	
Follow-up	**Days**	
range	28–1022	
mean	232	
Duration of surgery	**Minutes**	
range	16–140	
mean	48	

5.3 Occurrence of disturbance in surgical wound healing after operative treatment of zygomatic complex fracture and influence of dexamethasone (Study III)

Seventy-three patients fulfilled the inclusion criteria for Study III. Of these, 8 patients were excluded because they were lost to follow-up before the 30th postoperative day and one because the patient required further surgery due to an unsatisfactory fracture reduction. Thus, a total of 64 patients were followed up for at least one month. Descriptive statistics of the 64 patients are shown in Table 7.

Associations between DSWH and predictors are presented in Table 8. DSWH occurred in 9 patients (14.1%) on average 28 (range 7–92) days postoperatively. The clinical view of one of these patients is shown

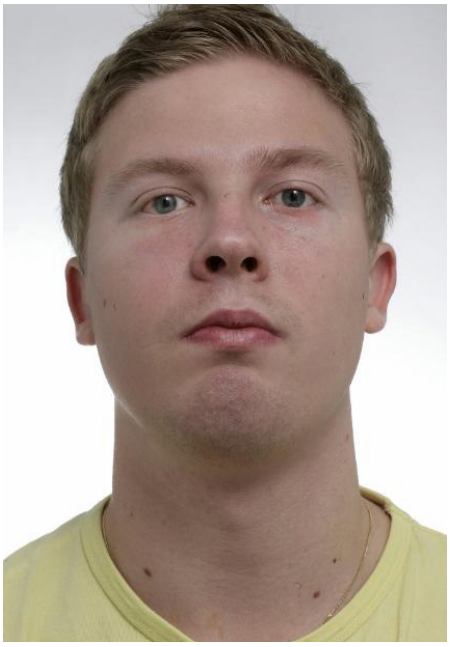

Figure 7. Clinical view of a patient with slight swelling, redness, and pain of the right cheek one month after repositioning and osteosynthesis of a zygomatic fracture. The patient received a total dose of 30 mg of dexamethasone related to surgery.

Table 8. Association between DSWH and predictor variables in 64 patients with zygomatic complex fractures (Study III).

	DSWH present	% of n
Gender		
male (n=46)	5	10.9
female (n=18)	4	22.2
p=ns		
Dexamethasone		
yes (n=33)	8	24.2
no (n=31)	1	3.2
p=0.016		
Total dose		
Dexamethasone 30 mg (n=22)	5	22.7
Dexamethasone 10 mg (n=11)	3	27.2
p=ns		
Surgical approach		
intraoral (n=34) *	7 *	20.6
exclusively extraoral (n=29)	1	3.5
p=0.042		
DSWH present (days postoperatively)		
range	7–92	
mean	28	
median	28	

*One patient with combination of intra-extraoral approaches is omitted because DSWH appeared in the upper eyelid.

DSWH: Disturbance in surgical wound healing

in Figure 7. DSWH occurred significantly more often in patients who received GCs (24.2%) than in those who did not (3.2%) (p=0.016). No dose-dependent effect between the total dose of 10 mg and 30 mg of DXE could be shown. In the DXE group, DSWH was established on average 30 days after surgery, the corresponding delay in patients not receiving DXE being 27 days (p=ns). The association between intraoral approach and DSWH was also significant (p=0.042). Figure 8 shows a patient with DSWH at the intraoral surgical site. Associations between DSWH and gender, time span from accident to surgery, age, and duration of surgery were non-significant.

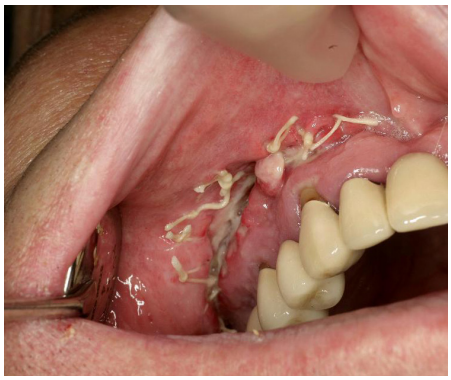

Figure 8. Intraoral wound dehiscence with infection one week after surgery of zygomatic fracture. The patient received a total dose of 30 mg of dexamethasone related to surgery.

5.4 Occurrence of pulp necrosis of teeth in the fractured area after operative treatment of mandibular fracture and influence of dexamethasone (Study IV)

Of the total of 41 patients with mandibular fractures in Study II, 24 fulfilled the inclusion criteria for Study IV. Descriptive statistics of these patients are shown in Table 9. None of the teeth in the fracture line had undergone endodontic treatment before the injury, none showed chronic infection, and none were fractured.

Associations between PN and predictors are presented in Table 10. PN was diagnosed in six patients (25%) and in 18.2% of the total of 33 teeth in contact with the fracture line. PN was diagnosed on average 115 (range 26–364) days after surgery. Four patients had one tooth with PN, and two patients had two teeth with PN.

PN occurred more frequently in patients who had received perioperative DXE (30.0%) than in those who did not (21.4%); however, the difference was not significant. In the DXE group, PN was established on average 168 days after surgery, the corresponding delay in patients not receiving DXE being 83 days (p=ns). Associations between PN and gender, age, smoking, and site of fracture were non-significant.

Table 9. Descriptive statistics of 24 patients with mandibular fractures in the tooth baring area (Study IV).

Age (years)		
range	18.1–50.9	
mean	29.2	
Gender	**No. of patients**	**% of 24**
male	23	95.8
female	1	4.2
Dexamethasone		
yes	10	41.7
no	14	58.3
Smoker		
yes	17	70.8
Fracture site		
body	2	8.3
symphysis/parasymphysis	10	41.7
symphysis/parasymphysis + angulus	10	41.7
body + angulus	2	8.3
Follow-up	**Months**	
range	3–19	
average	10	

Table 10. Association between pulp necrosis and predictor variables in 24 patients with mandibular fractures in the tooth-bearing area (Study IV).

	Pulp necrosis present No. of patients	**% of n**
Gender		
male (n=23)	6	26.1
female (n=1)	0	0
p=ns		
Dexamethasone		
yes (n=10)	3	30.0
no (n=14)	3	21.4
p=ns		
Smoker		
yes (n=17)	4	23.5
no (n=7)	2	28.6
p=ns		
Localization of pulp necrosis		
body (n=4)	0	0
symphysis/ parasymphysis (n=20)	6	30.0
p=ns		
Pulp necrosis present (days postoperatively)		
range	26–364	
mean	115	
median	72	

6. DISCUSSION

6.1 Methodological considerations

The occurrence of DSWH and the association between DSWH and DXE were analyzed retrospectively in 208 patients with different types of facial fractures (Study I) and prospectively in 41 patients with mandibular fractures (Study II) and in 64 patients with ZC fractures (Study IV). The occurrence of PN and its association with DXE were investigated in 24 patients with mandibular fractures. The patient numbers were deemed sufficient for meaningful statistical analysis.

The drop-out rates in Studies II and III were 8.9% and 12.3%, respectively. A 20% drop-out rate is generally accepted in follow-up of orthopedic trauma, and drop-out rates of 10% or less have been shown to be strongly reliable (Zelle, Bhandari et al. 2013).

6.2 Use of glucocorticoids in association with operative treatment of facial fractures

A survey of North American members of the American Society of Maxillofacial Surgeons evaluated the prevalence of use of GCs by surgeons performing craniomaxillofacial or esthetic surgery (Assimes, Lessard 1999). The results revealed that GC use was common; 46.7% of the respondents used short-term, high-dose GCs perioperatively. However, a great variety of preparations were used either alone or in combination, and the regimens were very heterogeneous. The most commonly reported GCs were DXE (60%) and methylprednisolone (56%), but also hydrocortisone (8%) and betamethasone (4%) were used. The total GC doses given, as equivalent to DXE, varied notably, and the total number of doses ranged from 1 to 22. Length of medication varied from 1 to 6 days. Also the present study revealed great variations in GC use (Study I). Three different preparations were used, the total number of doses varied from 1 to 3, the total doses, as equivalent to DXE, varied from 3.8 to 30 mg, and the total length of medication varied from 1 to 24 hours.

Several reasons exist for the marked variations in GC use among surgeons, the foremost being the lack of evidence-based recommendations. The only previously published randomized trial focusing on the effects of GCs in association with surgery of facial fractures came to the conclusion that a total dose of 1000 mg of methylprednisolone (equivalent to 190 mg of DXE) given as 4 doses of 250 mg every 6 hours is beneficial in reducing postoperative swelling after orbital surgery (Dan, Thygesen et al. 2010, Markiewicz, Brady et al. 2008, Flood, McManners et al. 1999). The total dose is notably higher than the maximum dose of 30 mg used in the present study. We did not aim to clarify the benefits of GCs in association with surgery of facial fractures, and therefore, it remains unclear whether the total dose of 30 mg of DXE is sufficient in reducing pain and edema. Moreover, facial fracture patients constitute an extremely heterogeneous group of fractures in terms of severity and extent and duration of treatment, so likely no all-inclusive regimen exists. Further studies are needed to determine optimal GC regimens for different types of facial fractures.

6.3 Occurrence of disturbance in surgical wound healing after treatment of facial fractures and influence of glucocorticoids

The findings of the present study revealed that GCs may indeed have an adverse effect on surgical wound healing. In patients with different types of facial fractures (Study I) and in those with mandibular fractures (Study II), the association between DXE and DSWH was not significant. However, an increasing trend towards DSWH in the DXE groups was observed, despite the fact that all patients received antibiotics perioperatively. In patients with ZC fractures, a significant association between DSWH and DXE emerged (Study III); perioperative DXE administration eight-folded the occurrence of DSWH. Therefore, perioperative DXE cannot be recommended in open reduction and fixation of ZC fractures.

In addition to DXE, also intraoral surgical approach was associated significantly with DSWH in patients with ZC fractures. A similar phenomenon was observed in a recent study of 177 patients with ZC fractures (Forouzanfar, Salentijn et al. 2013); of 9 wound infections, 8 occurred intraorally at the zygomatico-alveolar crest. In the present study, intraoral approach was a significant predictor for DSWH also in patients with different types of facial fractures (Study I). Moreover, all patients with mandibular fractures in Study II had been operated on with an intraoral approach, and the overall DSWH rate in these patients was notable (31.7%). The oral area in general and other local factors in particular, such as poor oral hygiene and poor clinical dental status, offer advantageous circumstances for bacterial infections. The results indicate that DXE should be used with caution in association with intraoral surgery of facial fractures, particularly if other local factors that increase the risk for wound infection are present.

Mastropietro et al. (2013) were the first authors to publish an association between increased cumulative duration of GC exposure and infection after pediatric cardiac surgery. The authors reviewed the files of 76 children, all of whom had received intraoperative methylprednisolone. Forty-eight percent had additionally received postoperative hydrocortisone and 86% periextubation DXE. Twenty-six children (36%) had postoperative infections that were significantly associated with days of GC exposure.

A similar trend was observed in the present study. DSWH was diagnosed in 6 of the 100 patients in Study I who had received GCs perioperatively. All 6 patients had received the maximal number of GC doses used in the study population, i.e., three DXE doses over 16 hours (Table 4). The biological half-life of DXE is 36–54 hours. Thus, repeated administration of DXE over the first days causes accumulation and prolongs the effects of the medication, thus increasing the risk for DSWH. With regard to surgical wound complications, a single dose of DXE is likely safer than multiple doses; however, further studies are required to assess this hypothesis, and also to clarify whether a single-dose regimen is sufficient to decrease the tissue reactions that cause postoperative discomfort.

An important finding of this study was the notable delayed occurrence of DSWH after surgery, being on average 47 days after different types of facial fractures (Study I), 31 days after mandibular fractures (Study II), and 28 days after ZC fractures (Study III). Overall, the longest delay of DSWH after surgery was more than 90 days. Moreover, in all three studies the delay was even longer when GCs had been used.

DXE may mask the signs of infection and inflammation, and therefore, clinical verification of local disturbances may occur with a lag. *Short-term DXE* decreases inflammatory mediator release effectively (Bronicki, Backer et al. 2000, Jansen, van Oeveren et al. 1991). It also lowers postoperative CRP levels, indicating a weakening of the immune response (Abdelmalak, Bonilla et al. 2013). Despite the low CRP levels, DXE does not reduce postoperative infective complications. In a randomized and controlled study of 381 patients having elective major non-cardiac surgery under general anesthesia, CRP levels were significantly lower in patients receiving perioperative DXE than in those who did not (Abdelmalak, Bonilla et al. 2013). However, the surgical site infections were even more frequent in patients receiving DXE (10.9% vs. 7.4%). In the present study, the delayed occurrence of DSWH in patients receiving DXE can be explained by the mask effect.

6.4 Occurrence of pulp necrosis of teeth in the fractured area after operative treatment of mandibular fracture and influence of dexamethasone

PN was found in 25% of patients and in 18% of teeth lying in the fracture line, figures that are lower than those observed by Oikarinen et al. (1990). In their study, the PN rate of teeth

in the fracture line was 38%. The higher rate can be explained by at least by three factors. First, the inclusion criteria were different. In the study by Oikarinen et al., angle fractures as well as teeth requiring endodontic treatment during surgery were included in the analysis. Second, the fractures were treated with intermaxillary fixation, a treatment method not used in the present study. Third, the follow-up time in Study IV was on average 10 months, in contrast to 43 months in the other study. Since PN can occur months or even years after the injury, we can assume that the occurrence of PN in our patients would have been higher had they been followed up for a longer period.

As was the case with DSWH, also PN occurred more often in patients who had received DXE. Moreover, the delay of PN was clearly longer after perioperative DXE. The findings emphasize that those patients who have teeth in the mandibular fracture line, in particular those who additionally receive perioperative GCs, should be referred to the general dentist for regular, long-term follow-up so that endodontic treatment can be initiated immediately when needed.

7. CONCLUSIONS

Study I revealed that GCs are commonly used by oral and maxillofacial surgeons in association with operative treatment of facial fractures. However, the regimens used are highly variable, likely because of the heterogeneity of the patients, who have injuries of varying severity and who undergo treatments of various extents and durations. Moreover, no evidence-based recommendations exist on the perioperative use of GCs.

Our subsequent studies showed that GCs may indeed cause complications at the surgical site. In patients operated on for ZC fractures (Study III), DSWH was significantly associated with perioperative use of DXE as well as with the intraoral surgical approach. In patients operated on for different types of facial fractures (Study I), DSWH was associated significantly with the intraoral surgical approach. In these patients, no significant association between DSWH and perioperative use of GC was found; however, DSWH occurred more frequently in the GC group. Also in patients undergoing intraoral surgery of mandibular fractures (Study II), DSWH occurred more frequently in the DXE group. The results show that perioperative DXE cannot be recommended in conjunction with surgery of ZC fractures. GCs should also be administered with caution in surgeries of other facial fractures, particularly when the intraoral approach is used.

Among patients with different types of facial fractures (Study I), those 6 patients who had received perioperative GCs and who ended up with DSWH had been administered the maximal number of GC doses used in the study population, i.e., three 10-mg doses every eight hours over 16 hours. With regard to surgical wound complications, a single dose of DXE is likely safer than multiple doses. However, further studies are required to assess this hypothesis and also to clarify whether a single-dose regimen is sufficient to achieve the desired effects of the medication, i.e., a decrease in the tissue reactions that cause postoperative discomfort.

In patients with different types of facial fractures (Study I), mandibular fractures (Study II), and ZC fractures (Study III), the delay of DSWH was notably longer in the DXE groups. Particularly PN (Study IV) was observed much later in the DXE group, on average 168 days after surgery. The findings emphasize that those patients who have teeth in the mandibular fracture line, in particular those who additionally receive perioperative GCs, should be referred to the general dentist for regular, long-term follow-up so that endodontic treatment can be initiated immediately when needed.

8. SUMMARY

1. The use of GC regimens in association with operative treatment of different types of facial fractures varied significantly. DSWH was observed in 3.9% of patients. It occurred more often in patients who received GCs than in those who did not (6.0% vs. 2.8%, p=ns).

2. DSWH was observed in one-third of mandibular fracture patients (31.7%). It occurred more often in patients who received GCs than in those who did not (35.0% vs. 28.6%, p=ns).

3. DSWH was observed in 14.1% of ZC fracture patients. It occurred significantly more frequently in patients receiving GCs than in those who did not (24.2% vs. 3.2%, p=0.016).

4. PN was observed in one-quarter of mandibular fracture patients (25.0%). It occurred more often in patients receiving GCs than those who did not (30.0% vs. 21.4%, p=ns).

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