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IS THERE A ROLE FOR PERIOPERATIVE USE OF DEXAMETHASONE IN FACIAL FRACTURE SURGERY? **ASPECTS IN POSTOPERATIVE NAUSEA AND PERIPHERAL NERVE RECOVERY**

Aleksi Haapanen

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To my family and friends

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their Roman numerals:

I Haapanen A, Thorén H, Törnwall J, Suominen AL, Snäll J. Postoperative nausea and vomiting in facial fracture patients: a randomized and controlled trial on the effect of dexamethasone. Int J Oral Maxillofac Surg. 2017 Oct;46(10):1267-1270.

II Haapanen A, Thorén H, Apajalahti S, Suominen AL, Snäll J. Does dexamethasone facilitate neurosensory function regeneration after zygomatic fracture? A randomized controlled trial. J Oral Maxillofac Surg. 2017 Dec;75(12):2607-2612.

III Haapanen A, Thorén H, Apajalahti S, Suominen AL, Snäll J. Neurosensory recovery after trauma to the orbital floor: a prospective trial with dexamethasone. Br J Oral Maxillofac Surg. 2018 Nov;56(9):810-813.

IV Haapanen A, Thorén H, Suominen AL, Snäll J. Does perioperative dexamethasone reduce neurosensory disturbance in mandibular fractures? A prospective 6-month follow-up trial. Submitted.

ABBREVIATIONS

5-HT	Serotonin
CINV	Chemotherapy-induced nausea and vomiting
CNS	Central nervous system
CTZ	Chemoreceptor trigger zone
GC	Glucocorticoid
IAN	Inferior alveolar nerve
IOF	Infraorbital foramen
ION	Infraorbital nerve
MMF	Maxillomandibular fixation
NASCIS	National Acute Spinal Cord Injury Study
NK-1	Neurokinin-1
NSD	Neurosensory disturbance
ORIF	Open reduction and internal fixation
PNS	Peripheral nervous system
PONV	Postoperative nausea and vomiting
RINV	Radiotherapy-induced nausea and vomiting
SAMBA	Society of Ambulatory Anesthesia
STN	Solitary tract nucleus
V_1	Ophthalmic branch of the trigeminal nerve
V_2	Maxillary branch of the trigeminal nerve
V_3	Mandibular branch of the trigeminal nerve
ZC	Zygomatic complex

ABSTRACT

Background and purpose

Glucocorticoids (GCs) are used in various medical indications. One generally accepted and well-known indication is perioperative administration to reduce postoperative nausea and vomiting (PONV). GCs are also used with mixed results in promoting nerve recovery after an injury. However, these two potential indications have not been extensively investigated in facial trauma populations. The aim of this study was to determine whether dexamethasone could reduce the incidence of postoperative nausea and vomiting PONV and promote nerve recovery in the trigeminal nerve area after a facial trauma.

Patients and methods

The study was based on a randomized controlled trial where patients were randomized to either receive dexamethasone or serve as a control. Study I included patients with different types of facial fractures (n=119), Study II patients with isolated zygomatic complex (ZC) fractures (n=64), Study III patients with isolated orbital fractures (n=18), and Study IV patients with one or two fractures in the dentate part of the mandible (n=27).

In Study I, the outcome variable was PONV and the primary predictor variable was the administration of perioperative dexamethasone. In Studies II-IV, the outcome variable was neurosensory disturbance (NSD) at 6 months and the primary predictor variable was the use of perioperative dexamethasone.

Results

The overall PONV incidence (Study I) was 16.8%. Dexamethasone did not reduce PONV incidence. In Studies II-IV, dexamethasone did not reduce long-term NSD. PONV was significantly more common in patients who received postoperative opioids. In Study III, a significant predictor for prolonged NSD was treatment delay.

Conclusions

The role of short-term dexamethasone in the indications studied remained insignificant. The findings therefore do not support the use of perioperative dexamethasone in reducing PONV or postoperative NSD in facial fracture patients. The low number of study subjects excluded the possibility for subgroup analysis.

1 INTRODUCTION

Glucocorticoids (GCs) have been used to treat various different medical indications, and due to their abundant pharmacologic actions possible indications for use are investigated continually. A known benefit of GCs is their potential to reduce nausea caused by various conditions. [1-4] The most common GC used is dexamethasone, and it is combined with other anti-emetics in high-risk individuals to prevent, for example, postoperative nausea and vomiting (PONV). [4,5]

PONV has been called a ”big little problem”. [6] This is because, although it is not a major life-threatening complication, the rate of PONV is around 50% and can as high as 80% in high-risk patients. [7] PONV causes delayed discharge from hospital, and it increases treatment costs due to prolonged treatment period and time lost from work. [8-10]

Studies on the use of GCs to induce nerve recovery have been conducted since the 1990s, and the main goal at the time was to enhance functional outcomes and hasten recovery after spinal cord trauma. [11,12] Although the efficacy of this treatment has later been questioned, interest in GC use in nerve recovery awakened. Furthermore, animal studies have shown some potential for GC use in neural trauma, but the implementation of these findings to clinical work has not been as promising as hoped. [13-16]

In this study, we aimed to clarify the potential benefits of GCs in reducing PONV and neurosensory disturbance (NSD) in a facial trauma population.

2 REVIEW OF THE LITERATURE

2.1 Trigeminal nerve and facial fractures

2.1.1 Overview of fractures

Fractures in the facial skeleton are common and are many times diagnosed in combination with concomitant injuries such as intracranial, limb, and vascular neck injuries. [17-19] The most common type of facial fracture is an isolated nasal bone fracture, others being fractures affecting the orbit and zygomatic complex (ZC) and mandibular fractures. [19-21]

2.1.2 Anatomy of the trigeminal nerve

The trigeminal nerve is the fifth cranial nerve and it consists of three main trunks, all of which subsequently form multiple smaller nerves. The main trunks are ophtalmic (V_1), maxillary (V_2), and mandibular (V_3). V_1 and V_2 are solely sensory nerves, whereas V_3 also has motor functions. [22]

V_1, V_2, and V_3 exit the skull through three separate foramina: the superior orbital fissure, the foramen rotundum, and the foramen ovale, respectively. From there, they innervate the mucosa and skin of the face from the forehead to the lower portion of the mandible (Figure 1). A large portion of the skin and mucosa of the anterior part of the lower face is innervated by two nerves: the infraorbital nerve (part of V_2), which rests on the orbital floor and exits the facial skeleton through the infraorbital foramen, and the inferior alveolar nerve (part of V_3), which passes through a bony canal in the mandible and exits the bone through the mental foramen as a mental nerve. [22,23]

Because of the routes of travel of the above-mentioned nerves, they are subject to injury in facial trauma. Fractures in the facial skeleton can pass through the foramina (as usually in the case of ZC fractures or parasymphysis fractures) or affect the bony canal, and therefore, the continuity of the nerve (in orbital blowout fractures or fractures affecting the inferior alveolar nerve (IAN) -bearing part of the mandible). This is why posttraumatic NSD in facial trauma patients is a good indication of a fracture. [24-27]

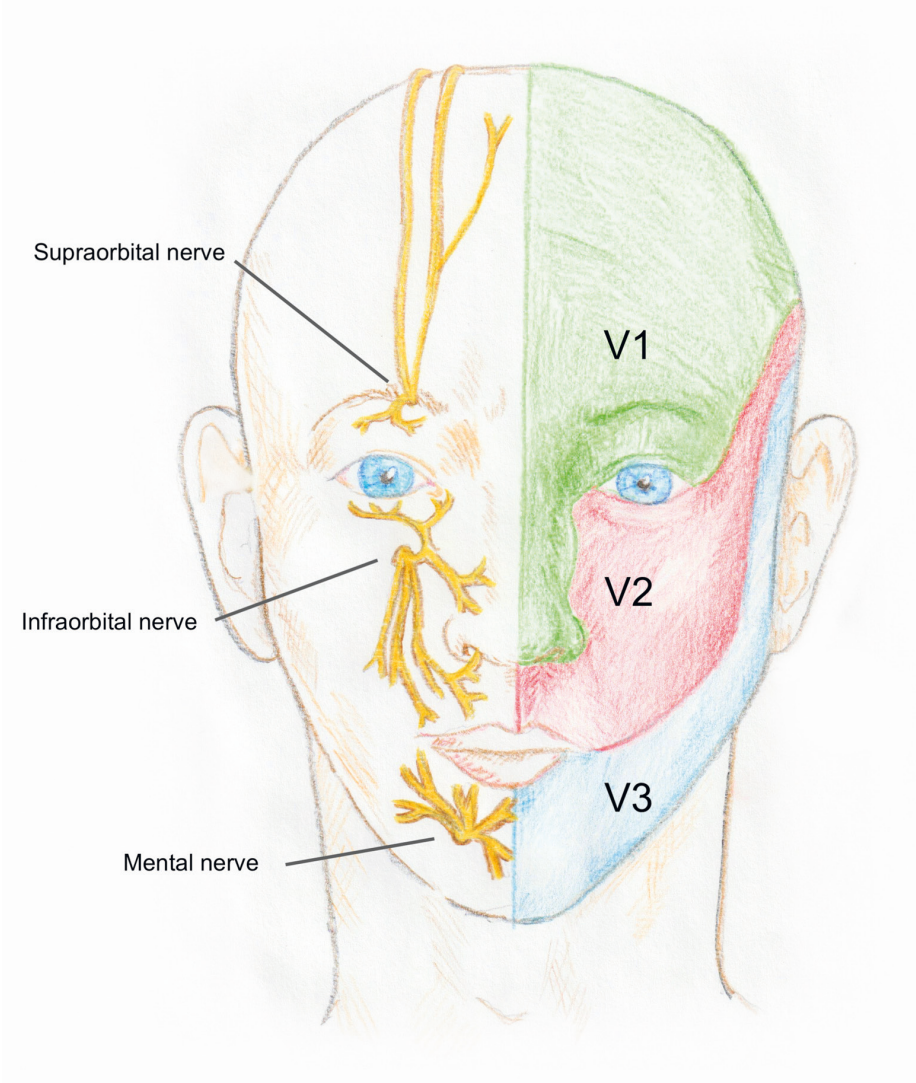

Figure 1. Trigeminal nerve and the area that it innervates.

2.2 Peripheral nerve tissue injury

Peripheral nerves consist of various soft tissue components (Figure 2). For example, the amount of connective tissue surrounding the nerve fibers varies depending on the need for protection. Nerves running in close proximity to the skin are subject to more physical stress and are therefore usually better protected by epi-, endo-, and perineural connective tissue, whereas nerves that are encapsulated in bony canals contain less connective tissue and are more likely to be damaged in a minor injury.[13]

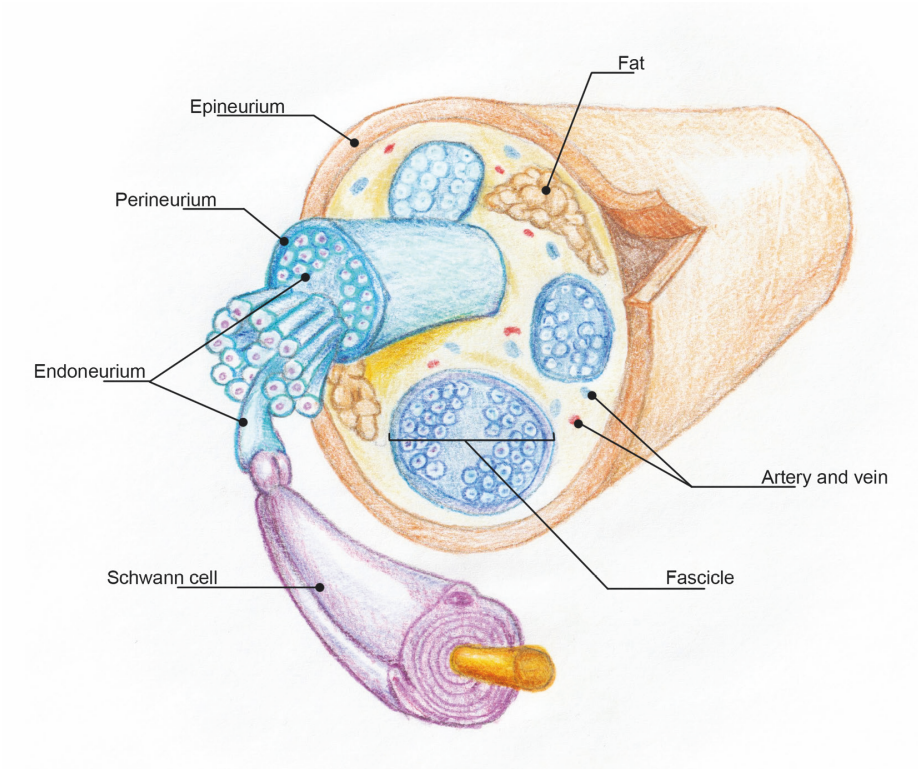

Figure 2. Anatomy of the nerve.

Peripheral nerve injury can be caused by various mechanisms. Damage can arise from mechanical compression, traction, or laceration,[28] endo- or exogenous ischemia, or any combination of these. Endogenous ischemia refers to ischemia of the small intraneural vessels that are located under the perineural sheet in the mixed connective tissue inside the nerve, whereas exogenous ischemia can be caused by compromised blood flow outside the nerve trunk. These different systems anastomose with each other, but also regulate the blood flow of the nerve independently. Acute short-term compression can result in nerve ischemia, hypoxia, increased vascular permeability, edema, and block of axoplasmic flow. A severe,

persistent compression has adverse effects on microcirculation.[29] Inflammation and infection can also cause peripheral nerve injury without any mechanical injury.[30-32] Additional possible causes for peripheral nerve injury include, among others, radiation, malignancy, toxins, and metabolic disorders.

As mentioned above, there are several different mechanisms for peripheral nerve injury. In traumatology, the nerve injuries are usually a combination of mechanical and ischemic injury. Mechanical injury is defined as an injury to the nerve trunk. This can be categorized according to the severity of injury and which tissues are affected. The two most commonly used classifications are by Seddon and Sunderland[33,34]. In 1943, Seddon described three basic types of nerve injury: Neurapraxia (Class I), Axonotmesis (Class II), and Neurotmesis (Class III).[33] In 1951, Sunderland expanded this classification and used a grading system (Grades I to V) to categorize these injuries.[34] Grades I and II correspond to Seddon's Class I and II. In Sunderland's classification, Seddon's Class III is divided into three different grades (III to V) depending on the severity of the injury. In 1998, Mackinnon and Dellon proposed that a Grade VI be added to Sunderland's classification to describe injuries that combine different grades of injuries.[35] Details of different types of neural trauma are shown in Table 1 and Figure 4.

Table 1. Nerve injury classification according to Sunderland[34] and Mackinnon & Dellon[35]

		Site of damage				
Grade	**Definition**	**Myelin**	**Axon**	**Endoneurium**	**Perineurim**	**Epineurium**
I	Neurapraxia	+				
II	Axonotmesis	+	+			
III	Neurotmesis	+	+	+		
IV	Neurotmesis	+	+	+	+	
V	Neurotmesis	+	+	+	+	+
VI	Combination	+/-	+/-	+/-	+/-	+/-

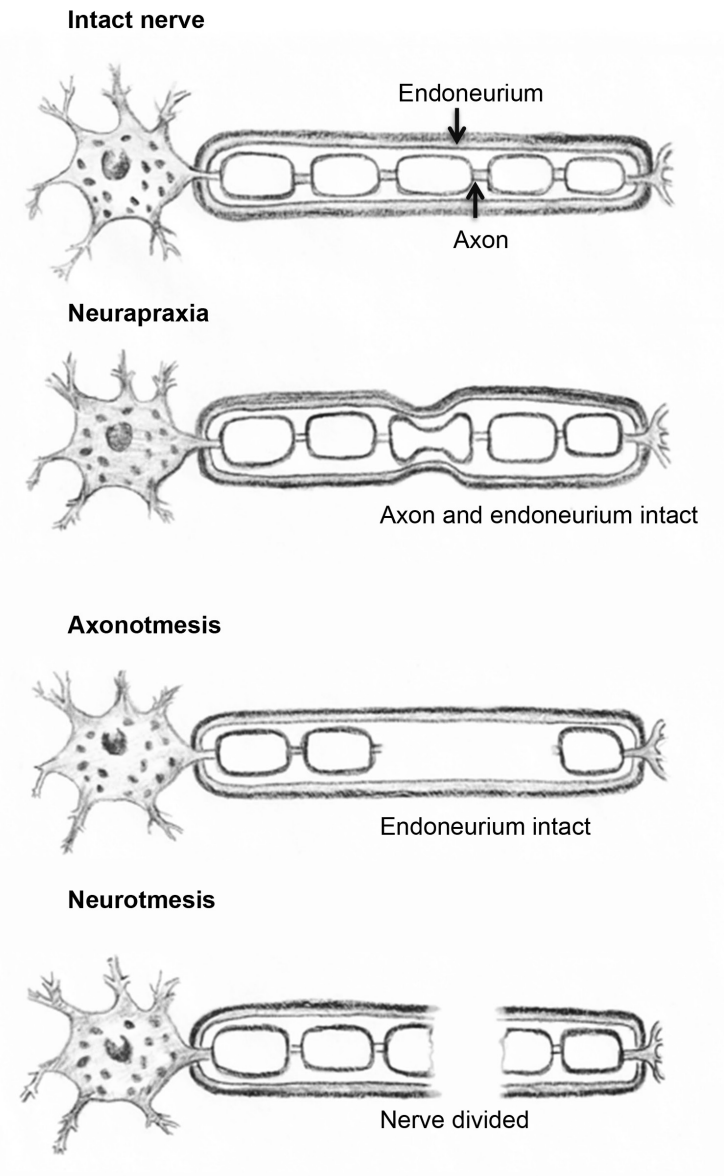

Figure 3. Different nerve injuries according to Sunderland.[34]

2.3 Recovery of different types of mechanical nerve injuries

The type and severity of mechanical injury has a significant effect on the recovery potential of the nerve. Type I compression injuries have the most favorable healing potential, whereas Type V transection injuries have very poor prognosis and usually require surgical intervention. [28] Various surgical methods have been used to treat these injuries with variable results. [36-39]

After an injury to axons and denervation of the end organ, regeneration of nerve function can happen in two different ways depending on the severity of the injury. If 20-30% of the axons are damaged, the healing can happen with collateral branching. This starts during the first 4 days after the injury and continues until 3-6 months. [28] If the injury is more severe and more than 90% of the axons within the nerve trunk are affected, the healing process is different. [40] In these cases, the primary mode of recovery is through axonal regeneration. This includes three different stages, all of which need to work in concert to achieve a favorable outcome; the distal stump of the axon goes through Wallerian degeneration, the axon regenerates, and finally re-innervation of the end organ occurs. [28,41,42] This healing process is largely mediated by Schwann cells. They trigger many key events in Wallerian degeneration and axonal regeneration by, for example, acting as phagocytes and recruiting macrophages, which are responsible for clearing of myelin debris and promoting the formation of new Schwann cells. [43-45]

2.4 Trigeminal nerve injury and neurosensory disturbance

Due to the anatomy of the trigeminal nerve and its peripheral branches, the nerve trunk is very often affected in surgery or trauma involving the facial skeleton. Most data published have concerned inferior alveolar nerve NSD in sagittal split osteotomies and lower third molar surgery. [46-49] In facial skeleton traumatology, the NSD can be caused by either the initial trauma or the surgery.

2.4.1 Posttraumatic neurosensory disturbance in midface fractures

Midface fractures often affect the infraorbital nerve (ION) and can potentially cause NSD in the area innervated by ION. This is common in ZC and orbital floor fractures, and it is worth noting that the vast majority of ZC fractures can be clinically diagnosed with a change in the neurosensory function. [50] In ZC fractures, 30-90% of patients suffer from posttraumatic NSD according to the literature. [25,51-55] Posttraumatic NSD rates in orbital floor fractures range from 11% to 93%, [56-59] and

9-55% of the patients operated on for orbital floor fracture still suffer from NSD at 6 months. [57,58,60] In rare cases, chronic pain can also occur, and this can cause profound problems in patients' daily lives. [61]

Despite the relatively large amount of data on ION injuries in facial trauma, the factors predicting NSD in orbital floor fractures remain unclear. A recent study in 2018 by Takahashi et al. examined orbital trapdoor fractures in adult and pediatric populations and found that posttraumatic NSD was significantly more common in adults (71% vs. 22%). [62] They hypothesized that the reason for this could be that adults have less soft tissue in the intraorbital foramen (IOF) region, which could then lead to a more prominent injury to the nerve in case of trauma. [62]

In ZC fractures, prognostic factors for NSD include a fracture passing through IOF and dislocation of more than 1 mm. [63-66] Isolated ZC fracture seems also to increase the risk for NSD compared with patients with multiple facial fractures. [63] Boffano et al. [63] also associated diplopia with NSD and discussed that this could be because of the larger trauma to the orbital floor.

2.4.2 Association between surgery and neurosensory disturbance in midface fractures

Scant data exist regarding the effect of surgery in NSD in midface fractures. Kloss et al. [67] reported in their large retrospective study in 2011 that there was more NSD in operated patients than in non-operated ones. However, they also stated that more displaced and comminuted fractures were operated on more often, and thus, the finding regarding NSD may be skewed.

Benoliel et al. [68] showed in their analysis that in ZC fractures open reduction and internal fixation (ORIF) was more beneficial than closed reduction without fixation in preventing postoperative NSD. The main finding was that electrical detection threshold was significantly lower in patients treated with ORIF. This means that patients treated with only a reduction without fixation needed a higher electrical current before they were able to sense the stimuli.

A few studies have attempted to determine whether surgery can help with posttraumatic NSD. [54,69] The idea is that a nerve is entrapped between bony fragments and by releasing pressure to the nerve with a reduction of the fracture, the nerve would regain its function more rapidly and more completely. The findings are, however, inconsistent and posttraumatic NSD cannot be considered an indication for surgical treatment in these cases.

There is also data that surgery itself can cause NSD. Peltomaa et al. [70] conducted a study in 2000 where they showed that surgery can indeed cause NSD in orbital floor and ZC fracture surgery. The data were gathered through a self-reporting questionnaire, and the conclusion was that at the end of follow-up, which ranged

from approximately 1 to 3 years, the non-treated group reported less NSD than the surgically treated group (26% vs. 47%).

2.4.3 Posttraumatic neurosensory disturbance in mandibular fractures

Unlike in midface fractures, there are some prospective studies about NSD in mandible fractures. Because of the anatomy of the mandible and the inferior alveolar nerve, it is meaningful to study NSD from two perspectives: IAN-bearing (fracture between lingula and mental foramen) and non-IAN-bearing (fracture between the mental foramina). Prospective studies show that in IAN-bearing fractures the posttraumatic NSD rate is 45-56%, postoperative NSD is 72.9-91.3%, and at 12 months 7.7-46.6% still suffer from NSD.[64,71-73] If the fracture is between the mental foramina (symphysis/parasymphysis fractures), the patients have significantly less posttraumatic NSD than in IAN-bearing fractures (12.6% vs. 56.2%).[72]

Patient-specific factors that correlate with an increased risk for posttraumatic NSD include age,[74] edentulous mandible,[71] and dislocation and comminution of the fracture.[64,72-75]

2.4.4 Association between surgery and neurosensory disturbance in mandible fractures

Some factors have been shown to correlate with postoperative NSD in mandible fracture patients. Edentulous mandible is a risk factor for posttraumatic but also postoperative NSD.[71] In edentulous patients with mandibular atrophy, the cross-sectional area of the nerve canal comprises a larger proportional area of the cross-section of the mandible, and therefore, the risk of accidentally damaging the nerve with screws or drill is greater. Fixation with two plates and inexperienced surgeon also correlate with a higher risk for postoperative NSD.[76]

2.5 Postoperative nausea and vomiting

2.5.1 Mechanism of nausea and vomiting

Nausea and vomiting can occur under various conditions and due to different stimuli. The most common causes for nausea include toxins, adverse drug reactions, disorders of the gut and peritoneum, endocrinological causes, psychiatric diseases, central nervous system (CNS) causes, traumatic events, and motion.[77-80] In general, the emetic reflex can be divided into two parts: the transmission of the emetic stimuli to the CNS and the vomiting response.

The emetic stimuli themselves can be initiated in the periphery or directly at the CNS. Depending on the stimuli, the following sites in the CNS are then activated:

- CNS above the medulla
  - Vestibular nuclei (vestibular system input)
  - Cerebral input
- Chemoreceptor trigger zone (CTZ) in the area postrema
- Solitary tract nucleus (STN)
  - Abdominal vagal afferents

These areas further activate the vomiting center, which initiates the vomiting response. Each of these locations has a specific purpose in transmitting and interpreting emetic signals, but the cause-effect relationship between these different parts of the CNS is not fully understood. The CNS above the medulla passes input from the inner ear, somatic sensation, and is also influenced by memory and emotions. CTZ is located at the bottom of the fourth ventricle and receives input from blood and cerebrospinal fluid. STN within the dorsal vagal complex gets input from the autonomic nervous system and the vagus and is thought to play a key role in gathering information and initiating the vomiting response. [77-79,81]

A vomiting response consists of the actual vomiting with vagus-mediated muscle contractions and prodromal activity such as respiratory and salivary activity, tachycardia, increase in blood pressure, cutaneous vasoconstriction, and sweating. [78,82] These symptoms mediated by the autonomic nervous system are well described in the literature by Horn et al. [82]

2.5.2 Pathophysiology of postoperative nausea and vomiting

Depending on the study, PONV is usually defined as an urge to vomit with or without successful (retching) expulsion of gastric contents during the first 24 hours after surgery. [83-85] PONV can be caused by various different causes. Some studies have shown that patients who undergo, for example, middle ear, eye, or strabismus surgery are at greater risk for PONV probably because of irritation of the trigeminal nerve and vestibular system. [86,87] However, Apfel et al. [85] did not find the type of surgery to be a significant factor in PONV in their large systematic review and meta-analysis of over 95 000 patients. Instead, they noted that the evidence was conflicting, as the reference groups in their analysis differed widely and funnel-plot analysis showed a significant publication bias. This does not, however, mean that the type of surgery could not play a key role in some instances.

Drugs used in surgery play a key role in PONV. Especially inhaled anesthetics, such as iso-, des-, and sevoflurane, have been shown to be a significant factor for developing PONV. [88,89] These drugs are thought to affect the CTZ directly, and

therefore, longer anesthesia time increases the risk for PONV. [89] Another major group of emetogenic drugs is opioids, which can cause nausea and vomiting through various mechanisms. They can directly irritate the CTZ and cause dizziness, thereby having an effect on the vestibular system, and they also cause ileus, which can then activate STN via abdominal vagal afferent nerves. [90]

2.5.3 Common risk factors for postoperative nausea and vomiting

Factors that increase the risk for PONV have been described by, among others, Apfel et al. [84,85] and Koivuranta et al. [91] In 2012, Apfel et al. conducted a meta-analysis of over 95 000 patients and concluded that the most reliable independent predictors of PONV were female gender (OR 2.57), history of motion sickness or previous PONV (OR 1.77), non-smoker (OR 1.82), younger age (OR 0.88 per decade), duration of anesthesia (OR 1.46), use of volatile anesthetics (OR 1.82), and postoperative opioids (OR 1.39). [85] Sinclair et al. showed in their study in 1999 that also surgery duration increases the risk for PONV significantly. They concluded that each 30-minute increase in duration increases the risk for PONV by approximately 60%. [83]

A convenient way to estimate a patient's individual risk for PONV is to use a risk score. One of the most common scores used is the one created by Apfel et al. [84] The Apfel score takes into account the four major risk factors for PONV: female gender, previous history of PONV or motion sickness, smoking status (non-smoker), and postoperative administration of opioids (Figure 4). The risk categories stratify 0–1 as "low", 2 as "medium", and 3 or more as "high". Although different risk scores are useful, it is important to note that they are not entirely predictive and only have a sensitivity and specificity between 65% and 70%. [7]

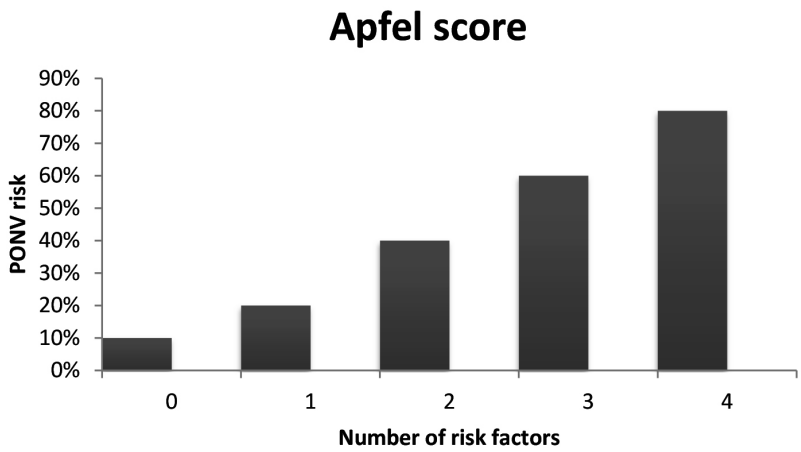

Figure 4. Association between PONV risk factors and PONV risk according to Apfel et al. [84]

2.5.4 Prevention and treatment of postoperative nausea and vomiting

In PONV prevention, it is important to take into account the patient-related risk factors and to minimize anesthesia- and operation-related risks whenever possible. Baseline risk can be reduced by avoiding general anesthesia and using local anesthesia when possible. Nitrous oxide and volatile anesthetics should be avoided and instead propofol should be used for induction and maintenance of anesthesia. PONV risk can also be managed by minimizing intra- and postoperative opioids and ensuring adequate hydration. [7] For example, avoiding nitrous oxide reduces the risk of PONV by 12%, and by using propofol rather than a volatile anesthetic the risk of PONV is reduced by 19%. [92]

Personalized PONV prevention is the gold standard. For patients at low risk, the PONV prevention should be assessed individually based on the procedure and cost benefit. For patients at moderate risk, the approach towards PONV prophylaxis should include a combination of two antiemetics, whereas for patients at high risk a multimodal approach is the method of choice. This should include two to three antiemetic drugs and, for example, opioid-sparing analgesia and propofol anesthesia. [5,7] An example of opioid-sparing analgesia is perioperatively administered non-steroidal anti-inflammatory drugs, which have been shown to decrease opioid-related PONV by 30%. [93]

Commonly used medications for prevention and treatment of PONV are shown in Table 2.

Table 2. Target mechanisms and example drugs for treating PONV. [7]

Target mechanisms	Example drugs
5-HT_3 receptor antagonists	Ondansetron
Neurokinin-1 (NK-1) receptor antagonists	Aprepitant
D_2-antagonists	Metoclopramide and Droperidol
Corticosteroids	Dexamethasone
H_1-receptor antagonists	Promethazine
Anticholinergics, i.e. muscarinic receptor antagonists	Scopolamine (transdermal)

The above-mentioned antiemetic drugs are used alone or as a combination of two or more. Combination therapy is preferred especially in patients with a high risk for PONV, as the effects of antiemetics acting via different receptors are additive, and therefore, in case the prevention fails the rescue drug should preferably be chosen from a different drug group. [5] An overview of the different receptors and commonly used antiemetics is shown in Figure 5.

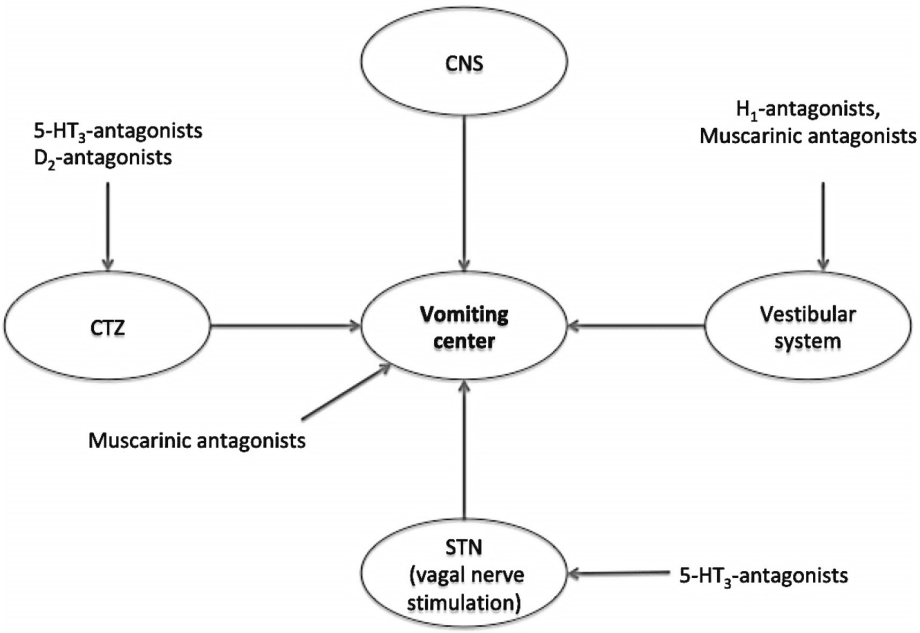

Figure 5. Target areas of some of the most commonly used antiemetics.
(CNS = central nervous system; CTZ = chemoreceptor trigger zone; STN = solitary tract nucleus). Modified from *Nausea: a review of pathophysiology and therapeutics* by Singh et al. [80]

2.5.5 Postoperative nausea and vomiting after maxillofacial surgery

Studies regarding PONV after maxillofacial surgery are scarce, and most of the studies cover PONV after orthognathic surgery. Overall, the incidence has been reported to lie between 12.5% and 67%. [94-99] Patients undergoing orthognathic surgery and especially surgery to the maxilla are at greater risk for developing PONV. [94,95,100]

Only a few studies have examined PONV in maxillofacial trauma populations among other oral and maxillofacial populations. Laskin et al. [99] sought to clarify the risk factors in oral and maxillofacial surgery and to determine whether the Apfel score [84] was useful in oral and maxillofacial surgery to predict PONV. This retrospective study included a total of 167 patients, 28 of whom were facial trauma patients. The overall PONV rate was 24%, and it was significantly different between different surgery types. In the facial trauma population (n=28), the PONV rate was 14%. Laskin et al. found that orthognathic and temporomandibular joint surgery, young age, and maxillomandibular fixation (MMF) were significant risk factors for PONV. Interestingly, the predictability of postoperative vomiting by using only these three predictors (surgery type, MMF, and young age) was 0.75 (predicted 75%

of PONV risk), which was actually more accurate than adding these two predictors to the Apfel risk score predictors (0.74), and they proposed adding the use of MMF, age, and surgery type to the Apfel score to improve its value in oral and maxillofacial surgery when predicting PONV. [99] The number of facial fracture patients in this study was small, and it did not differentiate the types of maxillofacial trauma. The data were also gathered retrospectively, and the perioperative drug regimen was not controlled. Thus, there is a need for further prospective studies regarding PONV in maxillofacial trauma populations.

Albuquerque et al. [98] found in their prospective analysis of 145 facial trauma patients that the PONV correlated with intraoral access, obesity, anesthesia duration, surgical procedure duration, and length of hospital stay. Also patients in their second or fourth decade were at risk for PONV. Their study also confirmed earlier findings that female sex, history of PONV, and use of opioids were risk factors for PONV.

2.6 Basic pharmacologic actions of glucocorticoids and common side-effects

2.6.1 Basic pharmacologic actions of glucocorticoids

GCs have various different actions and they play a key role in regulating metabolism, immune system, and development and differentiation of organs. GCs increase glucose levels by increasing gluconeogenesis and inhibiting glucose uptake by various tissues. They also increase lipolysis and promote protein metabolism. GCs suppress the immune system and inflammatory response by decreasing the number of circulating lymphocytes, decreasing the production of anti-inflammatory agents, such as prostaglandins and leukotrienes, and inhibiting fibroblast proliferation. [101]

GCs bind to different plasma proteins in the blood and they target cells mostly via GC receptors, which are found in nearly every human cell and directly or indirectly regulate gene transcription. The target gene can be transactivated or transdepressed; [102] the former is usually linked to various adverse effects, whereas the latter is responsible for desirable anti-inflammatory and immunosuppressive effects. [103,104] In addition, GCs have non-specific and non-genomic interactions with, for example, cellular membranes and cytosolic GC receptors. These types of interactions are usually more rapid than genomic interactions. [105]

It is important to differentiate elimination half-life and biological half-life of GCs. Elimination half-life is the amount of time required for half of a drug's concentration to disappear from plasma, whereas the biological half-life refers to the duration of effect. The biological half-life of GCs is usually longer than the elimination half-life

because many GCs' effects are due to alterations in genetic regulation of protein production. This is also the reason for the slow onset of various effects of GCs. [106]

Synthetic GCs are used to mimic the effect of human cortisol, which is synthesized in the adrenal cortex, and a suitable synthetic GC is chosen for a specific need according to their pharmacokinetic and pharmacodynamic properties (Table 3).

Table 3. Potencies of different glucocorticoids.

Glucocorticoid	Anti-inflammatory potency	Relative glucocorticoid activity	Biological half-life (h)	Equivalent dose (mg)
Cortisol (Hydrocortisone)	1	1	8-12	100
Cortisone	0.8	0.8	8-12	125
Prednisone/ Prednisolone	4	4	12-36	25
Methylprednisolone	5	5	12-36	20
Triamcinolone	5	5	12-36	20
Betamethasone	25	20-30	36-54	4
Dexamethasone	25	20-30	36-54	4

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

2.6.2 Drawbacks of glucocorticoids

GCs have various pharmacologic actions, and therefore, the possible adverse effects are also numerous, especially with prolonged use. Skin and muscle atrophy, osteoporosis, steroid psychoses, electrolyte and metabolism imbalances (such as diabetes mellitus and Cushing's syndrome), hypertension and dyslipidemia, and gastrointestinal issues, such as peptic ulcers and pancreatitis, are among many known side-effects of long-term GC use. [107-109]

Short-term GC use also has some well-documented drawbacks, although the side-effects are dose- and time-dependent. Short-term use has been shown to cause hyperglycemia and impaired insulin sensitivity, changes in metabolism of energy stores, lymphopenia, and disruptions in cognition, mood, and sleep in a hypomanic manner. [110-113] Short-term GCs can also cause disturbance in surgical wound healing [114] and make it harder to assess early systemic infections, as it decreases blood CRP and induces leukocytosis. [115,116] Overall, the side-effects are less severe in short-term use than over a longer period. [109,112]

2.6.3 Use of glucocorticoids to prevent postoperative nausea and vomiting

At the beginning of the 1980s, studies were published showing that dexamethasone reduced chemotherapy-induced nausea and vomiting,[1] and studies in the following decades have found that dexamethasone and related GCs can also help reduce PONV.[2,3,117] The Society of Ambulatory Anesthesia (SAMBA) recommends dexamethasone for preventing PONV,[7] and a large systematic review concluded that the efficacy of dexamethasone in reducing PONV is equivalent to that of ondansetron.[118]

Mechanism of glucocorticoids

The exact mechanism of how GCs reduce PONV is unclear. There are, however, multiple theories to explain the reduction in PONV incidence.

In studies regarding chemotherapy and radiotherapy, there is evidence that anti-inflammatory drugs can reduce chemotherapy-induced nausea and vomiting (CINV) and radiotherapy-induced nausea and vomiting (RINV).[119,120] The reason for this could be that the destruction of cells releases inflammatory mediators, which then could induce nausea, and administering anti-inflammatory drugs could reduce this effect.[81] Inflammatory agents can also trigger pain and lead to excessive use of opioids. Opioids, in turn, can cause nausea and vomiting or ileus, which itself is a known risk for nausea.[121-125]

Another possible mechanism is the ability of GCs to reduce serotonin (5-HT) levels. Serotonin is a neurotransmitter that has been shown to cause nausea[126,127]. GCs could both reduce the release of 5-HT from peripheral mononuclear cells[128] in humans and directly inhibit 5-HT_{3A} -receptors *in vitro,*[129] thereby having a positive effect on nausea and vomiting.

GCs are essential for the functioning of organs, and they are especially important under stress conditions.[130] GC deficiency has been shown to cause nausea and vomiting under such stress as chemotherapy.[131] If the stress is overwhelming or the patient is in a hypocortisol state, administering exogenous GC could reduce emesis.

Efficacy of glucocorticoids

Dexamethasone and other GCs are usually used in combination with other antiemetics, and the combination most used is intravenous administration of dexamethasone and ondansetron.[5,118] These two drugs combined can help reduce 1 in every 4 early PONV cases (within the first 6 hours after operation) and 1 in every 5.5 late PONV cases.[5,118] Patients who receive combined prophylaxis for PONV are also less likely to suffer from PONV than patients with monotherapy prophylaxis ($5HT_3$-antagonist or GC alone).[132]

Dosage and timing of glucocorticoids

The optimal dose of dexamethasone in PONV prophylaxis has been studied in recent years. De Oliveira et al. [133] showed in their meta-analysis of 6696 subjects undergoing a large variety of different surgical procedures that there is no difference in the antiemetic effect of dexamethasone when used as an only antiemetic or in combination in doses between 4-5 mg i.v. and 8-10 mg i.v. Ho et al. [134] came to a similar conclusion in their study on women undergoing abdominal total hysterectomy under epidural anesthesia. They did not find difference in PONV reduction between doses of 5 mg i.v. and 10 mg i.v. [135] At the moment, the recommended dosage for dexamethasone in adults for PONV prophylaxis according to SAMBA guidelines is 4-5 mg i.v. [7,135,136]

Timing of the administration is also paramount when using dexamethasone and other GCs in reducing PONV. Studies have shown that it takes approximately 2 hours for the antiemetic effect of dexamethasone to begin, and if administered at the end of anesthesia the efficacy is not as good as when administered at induction. [2,137] Intravenous dexamethasone has a slow onset time and a long duration, and it can take up to 12-24 hours to achieve the maximum effect. [138] The reason for the slow onset is the molecular mechanism by which GCs affect gene transcription of cells. [103] Bearing this in mind, dexamethasone is better used as PONV prophylaxis than as a rescue drug.

2.7 Short-term glucocorticoids in surgery and trauma

Short-term GC treatment usually refers to treatment lasting up to 7 days. The dosages are ordinarily higher and the administration is intravenous or intramuscular compared with longer-term use, where the route of administration is more often oral or local.

2.7.1 Notable indications for glucocorticoid use in surgery

As mentioned earlier, GCs have been shown to reduce postoperative pain and the need for rescue analgesics after third molar extraction. GCs have also been used to reduce pain in other fields of surgery. De Oliveira et al. [133] published a systematic review and meta-analysis of 24 randomized controlled trials in 2011 where they investigated the effect of intraoperative dexamethasone in reducing postoperative pain in various types of operations (e.g. laparoscopic operations of the abdomen, total hip arthroplasty, nasal sinus endoscopy). They concluded that intermediate to high doses (>0.1 mg/kg) had an opioid-sparing effect after different types of surgery procedures. Diakos et al. [121] came to the same conclusion in their meta-

analysis of 580 adult tonsillectomy patients treated with dexamethasone, although they could not specify the optimal dose.

In anesthesiology, GCs are also used to reduce intubation-related complications, such as postoperative sore throat and laryngeal edema, with good results. [139,140] According to a large meta-analysis of 2685 patients by Zhang et al. [140] in 2016, prophylactic GC reduced laryngeal edema after intubation and also significantly reduced the need for reintubation. Pehora et al. [141] concluded in their systematic review of 2702 patients that there is low-to moderate-quality evidence that dexamethasone as an adjuvant to peripheral upper limb nerve block can reduce pain and postoperative opioid consumption. In 2019, Marhofer et al. [142], however, did not find dexamethasone to affect the duration of sensory block when administered as an adjuvant to ropivacaine.

Overall, GCs have been shown to reduce many surgery and anesthesiology-related complications and side-effects.

2.7.2 Use of glucocorticoids in central nervous system trauma

GCs have been in the past decades widely used to potentially enhance functional outcomes and speed the recovery after a spinal cord trauma. High-dose methylprednisolone was the drug of choice according to the National Acute Spinal Cord Injury Study (NASCIS) published in the New England Journal of Medicine in 1990 and the Cochrane Review published in 2012. [11,143] Further studies in the last five years have, however, questioned the efficacy and safety of this treatment, and the current consensus is that GCs should not be used to treat acute traumatic spinal cord injuries. [144,145]

In ophthalmology, steroids are used to treat optic neuritis. They have been shown to shorten the period of acute visual dysfunction, but they do not affect the final visual outcome. [146,147] Optic neuritis is a non-traumatic inflammatory condition, and it is therefore logical that anti-inflammatory drugs can have a positive impact. In traumatic optic neuropathies, however, the efficacy is very controversial. [147,148] The hypothesis behind the potential positive effect in traumatic optic neuropathies comes from the same NASCIS study mentioned above, and given the fact that these findings have since been questioned, it is easy to understand the uncertainty in using GCs to treat traumatic optic neuropathies.

2.7.3 Glucocorticoids in peripheral nervous system trauma and regeneration

GCs are used in a variety of peripheral mononeuropathies with good results. Carpal tunnel syndrome is treated with steroid injections and oral GCs in mild to moderate stage conditions where they are especially helpful in reducing pain symptoms. [149,150]

A recent randomized controlled trial published in Lancet in 2018 showed that a single corticosteroid injection provided superior clinical effectiveness at 6 weeks compared with night-resting splints, making it the treatment of choice for a rapid symptom response. [151]

The pathophysiological mechanisms of anti-inflammatory agents in neuropathies remain largely unknown. Animal studies have been trying to answer this question, and some promising findings have emerged. Al-Bishri et al. [13] and Mohammadi et al. [14] arrived at the conclusion that both systemic betamethasone and topically administered dexamethasone could have a positive effect on the healing potential of a crushed sciatic nerve in rats. [13,14] Endogenous GCs are also established to play a key role in activating Schwann cells, improving the myelination process. [152] They also inhibit nuclear factor kappa B, which is closely related to inflammation, and this inhibition significantly improved nerve regeneration in adult rat models. [153]

2.7.4 Glucocorticoids in maxillofacial surgery

Short-term GCs have been widely studied in both oral and maxillofacial surgeries to prevent pain, swelling, and trismus (limited mouth opening) in particular. [154-160] The most prominent data have been derived from lower third molar surgery, as it is a common procedure with a possibility for a split mouth study (use one lower third molar as an intervention group and the other as a control in the same patient), and multiple systematic reviews and meta-analyses have been conducted. The administration routes in these studies have been either local (intramuscular or submucosal injection to the tissue next to the surgical site) or systemic (oral or intravenous). Overall, the consensus in the literature is that regardless of the administration route, GCs have a positive effect in reducing postoperative pain and swelling, but data on local administration in reducing postoperative trismus are limited. [154-160]. Preoperative administration is superior to postoperative, [156,159] but the ideal intramuscular dose is still under debate. [154] Other than the submucosal route, all administration routes seem to be equal in efficacy. [156]

GCs have also been used with positive results in orthognathic surgery to reduce postoperative edema [16,161-164] and pain. [162] For example, de Lima et al. [161] showed in their systematic review that the use of GCs reduces postoperative edema after orthognathic surgery independent of the dose used compared with the control group. Dan et al. [162] revealed in their meta-analysis in 2010 that GCs significantly reduce postoperative pain in orthognathic surgery. The estimated relative rate of analgesia with GCs was 2.88 compared with placebo.

A large systematic review of 31 studies on the role of corticosteroids in cervicofacial infections concluded that GCs are effective in reducing, for instance, edema, pain, and hospital stay. [165] The study also concluded that GCs are relatively

safe to use. However, the researchers did not find any studies on GC use in odontogenic head and neck infections. [165]

Limited data exist on the use of GCs in oral and maxillofacial trauma surgery. Dongol et al. [166] conducted a prospective randomized controlled double-blind study in 2015 where they used 8 mg of submucosal dexamethasone in patients undergoing ORIF of mandibular fracture. They concluded that submucosal injection of dexamethasone reduced postoperative pain and edema. The study group showed more postoperative infections and fever, but this difference was not statistically significant.

A few recent studies have examined the role of GCs in maxillofacial surgery in particular. Kormi et al. [167,168] found dexamethasone to be useful in postoperative pain management in patients treated for ZC or orbital fractures. Kainulainen et al. [169] also came to a similar conclusion in their study of patients undergoing microvascular reconstructive surgery due to head and neck cancer [169]. They showed that the need for postoperative opioids was significantly less in patients who received dexamethasone. The use of postoperative oxycodone during the first 24 hours was 81.2 mg in the study group and 112.1 mg in the control group.

3 AIMS OF THE STUDY

The aim of this study was to investigate the usefulness of perioperatively administered high-dose dexamethasone in patients undergoing treatment for facial fractures.

Specific aims were as follows:

1. To determine the occurrence of PONV in patients with different types of facial fractures and to evaluate the use of dexamethasone in reducing PONV (I).

2. To determine the occurrence of NSD in patients surgically treated for ZC and orbital floor fractures and to evaluate the effect of dexamethasone in enhancing recovery of NSD of ION (II and III).

3. To determine the occurrence of NSD in patients surgically treated for mandibular fractures and to evaluate the effect of dexamethasone in enhancing recovery of NSD of IAN (IV).

4 PATIENTS

4.1 Study design

A randomized study with dexamethasone in facial fracture patients was conducted between January 1st 2006 and December 31th 2010 in the Department of Oral and Maxillofacial Diseases, Helsinki University Central Hospital, Helsinki, Finland. The study population consists of patients over 18 years of age undergoing an open reduction of a fracture in the zygomatic complex, orbit, or mandible. Patients with infected fractures or those pregnant or breastfeeding were excluded from the study. Also an allergy to any component used in the dexamethasone preparation, history of psychosis due to use of GCs, peptic ulcer, and kidney or liver dysfunction served as exclusion criteria.

Study populations in Studies I-IV were extracted from this group of patients.

4.2 Surgery protocol

Patients were surgically treated under general anesthesia. All of the mandibular fractures were fixated with 2.0 mm titanium miniplates according to Champy's principles. ZC fractures were treated with open reduction with or without miniplate fixation depending on the stability of the fracture, and orbital-fractures were reconstructed with titanium mesh or bone graft. Throat pack was used in intraoral surgery to minimize blood leaking to the digestive tract.

4.3 Perioperative drug regimen protocol (I-IV)

Patients were randomized into two groups using sealed envelopes. The patients in the study group received dexamethasone (Oradexon®, 5 mg/ml injection solution, Orion Pharma, Espoo, Finland), while patients in the control group received no GC or placebo.

All of the patients in the study group received 10 mg of dexamethasone at the induction of anesthesia. Twelve ZC fracture patients were part of a pilot study and received only the 10 mg of dexamethasone (part of the study cohort in Study II), whereas all of the other subjects in the study group received an additional 10 mg of dexamethasone intramuscularly every 8 hours over 16 hours for a total dose of 30 mg of dexamethasone (Studies I-IV).

Anesthesia was initiated using propofol and maintained with sevo- or desflurane. Fentanyl was used as an analgesic during the surgery. Each patient received 0.1-0.2 mg of fentanyl during induction of anesthesia. During surgery a bolus of fentanyl (0.05-0.1 mg) was given if the patient´s heart rate and/or systolic blood pressure increased by 15%. Basic postoperative pain relief was provided with 1 g of paracetamol every 6 hours, and intravenous oxycodone (0.02-0.04 mg per 1 kg) was used at the recovery ward, followed by 0.1 mg per 1 kg intramuscularly in the inpatient ward when needed. Ondansetron was not used routinely, but served as rescue medication for PONV when needed.

All patients in Studies I-IV were administered postoperative antibiotics: intravenous cefuroxime 1.5 g three times a day during the first 24 hours, followed by three daily doses of 500 mg of oral cephalexin until the seventh to tenth postoperative day. In patients with allergies to these substances, alternative antibiotics via corresponding routes were used.

4.4 Clinical evaluation

4.4.1 Evaluation of PONV (I)

PONV was evaluated during the first 24 hours postoperatively. Enquiry by a nurse was done every 6 hours and every time oxycodone was administered. Retching and vomiting occurring on other occasions were also registered. PONV was recorded as positive when a patient complained of symptoms of nausea or if a patient vomited.

4.4.2 Sensory evaluation (II-IV)

NSD was tested by one examiner using touch and pinprick in the areas of the skin and mucosa innervated by ION (Studies II and III) or IAN (Study IV). Sensation was tested with a sharp and a dull instrument (sharp and dull ends of a dental sond) and compared with the contralateral side to find differences in subjective sensory functions. Sensory function was reported as NSD if the patient reported abnormal sensation during the test. The examiner was blinded to dexamethasone.

4.4.3 Follow-up (II-IV)

Follow-up was arranged postoperatively at 1, 3, and 6 months. The sensory evaluation protocol was done in the same manner as in the primary evaluation by a blinded examiner using the aforementioned criteria for NSD. A longer follow-up was arranged for surgical reasons when needed.

4.5 Study populations

In Study I, all patients included in the randomization were analyzed.

In Study II, all patients with ZC fractures with ipsilateral preoperative NSD and a follow-up of one month were included in the analysis.

Study III comprised patients with an isolated unilateral orbital floor fracture with or without medial wall fracture and with either pre- or postoperative NSD. A follow-up of 6 months was required for patients to be included in the analysis.

Study IV comprised patients with a single unilateral fracture in either the symphysis/parasymphysis region (non-IAN-bearing) or in the angle or corpus of the mandible (IAN-bearing) or a double fracture in the dentate portion of the mandible and with postoperative NSD. Patients with a parasymphysis fracture passing through the foramen were excluded. A follow-up of 6 months was required for patients to be included in the analysis.

5 METHODS

5.1 Outcome variables

Primary outcome variables were PONV (Study I) and postoperative NSD at 1 month (Study II), 3 months (Study II), or 6 months (Studies II-IV).

PONV was recorded when the patient suffered from nausea or vomiting during the first 24 hours postoperatively. PONV was recorded as positive when the patient complained of symptoms of nausea or if the patient vomited.

Primary outcome variable in Studies II-IV was NSD in the area innervated by either ION (Studies II and III) or IAN (Study IV). Sensory function was reported as NSD if the patient reported abnormal sensation during the test.

5.2 Predictor variables

The primary predictor variable was perioperative use of dexamethasone (I-IV). Secondary predictor variables were age and gender (I-IV), timespan from accident to surgery (II-IV), site of fracture (I, IV), surgical approach (I, II), injury mechanism (II), duration of anesthesia (I), postoperative administration of opioids (I), and radiological features of fractures (II, III).

5.2.1 Clinical predictors

Timespan from accident to surgery was defined as days from time of initial trauma to day of surgery (II-IV).

Site of fracture was defined in Study I as either an isolated ZC or orbital fracture or one or more fractures in the dentate part of the mandible. In Study IV, the site was defined as either an IAN-bearing (angle or body of mandible) or a non-IAN-bearing (symphysis/parasymphysis) fracture.

Surgical approach was considered an intraoral approach in Studies I and II if intraoral incision was used either alone or in combination with extraoral incision.

Injury mechanism was used as a predictor in Study II. It was categorized as assault, traffic, fall, sports, or other.

Duration of anesthesia was used as a predictor in Study I, and it was measured in minutes from the induction to the end of anesthesia.

Postoperative administration of opioids was used as a predictor for PONV in Study I, and it was recorded when a patient needed postoperative opioid medication for pain after admission from the operating room to the recovery room and ward.

5.2.2 Radiological predictors

In Studies II and III, a senior oral and maxillofacial radiologist evaluated the preoperative computer tomography (CT) twice at a two-week interval in a blinded manner.

In Study II, the relation of the fracture to the IOF was categorized as follows: 1) no fracture through the foramen, 2) fracture through the foramen without impression or comminution, and 3) fracture through the foramen with impression and/or comminution.

In Study III, the CT data were reformatted as parasagittal to orbit. The original image slices were 1.0 or 1.5 mm thick. The maximum displacement of the orbital floor and of the ION (in mm) was evaluated and recorded. A zone qualification by Jaquiery et al. [170] was used to assess the anterior-posterior depth of the fracture. In this qualification, the orbital floor is divided into three zones, with the most anterior being Zone 1 and most posterior Zone 3. The maximal zone where the fracture extended was recorded.

In Study IV, the relation of the fracture to the mental foramen was assessed from a dental panoramatomographic image by a trained oral and maxillofacial surgeon. Patients with a fracture passing through the mental foramen were excluded.

5.3 Statistics

Chi-square (SAS 9.4, SAS Institute Inc., Cary, NC, USA) was used to evaluate associations and significances between outcomes (PONV in Study I, NSD in Studies II-IV) and predictor variables. Mann-Whitney U–test (SAS 9.4, SAS Institute Inc., Cary, NC, USA) was used to evaluate differences between continuous variables, including age (I-IV), timespan from accident to surgery (II-IV), and duration of anesthesia (I). Significance level was set at 0.05.

Two-sided Fisher exact test with a significance level of 0.05 was used for a retrospective power analysis for a test of the two independent proportions, namely occurrence of PONV/NSD and perioperative use of dexamethasone.

5.4 Ethical considerations

The study protocol was approved by the Ethics Committee of the Department of Surgery and the Internal Review Board of the Division of Musculoskeletal Surgery, Helsinki University Hospital, Finland (Dno 33/E6/06) and registered at the Helsinki University Hospital, Helsinki, Finland under identification number HUS2325. The study has since been approved by the Internal Review Board of the Head and Neck Center, Helsinki University Hospital, Helsinki, Finland (356/2017).

The study protocol was in accordance with the 1964 Declaration of Helsinki and amendments thereafter. The Finnish National Agency for Medicines was informed about the study. Written informed consent was obtained from all participants.

6 RESULTS

6.1 Dexamethasone in preventing postoperative nausea and vomiting in facial fracture patients (Study I)

Altogether 129 patients underwent surgery for facial fracture reduction or orbital fracture reconstruction (Figure 6). Seven of these patients did not consent to participate in the study and three were excluded because they did not comply with the dexamethasone dosage regimen. Thus, 119 fulfilled the inclusion criteria and were included in the analysis. A total of 59 patients (49.6%) were randomized into the study group and received perioperative dexamethasone. Descriptive statistics of the patients are shown in Table 4.

Altogether 20 patients (16.8%) suffered from PONV, 95% of whom experienced it during the first 12 h after surgery.

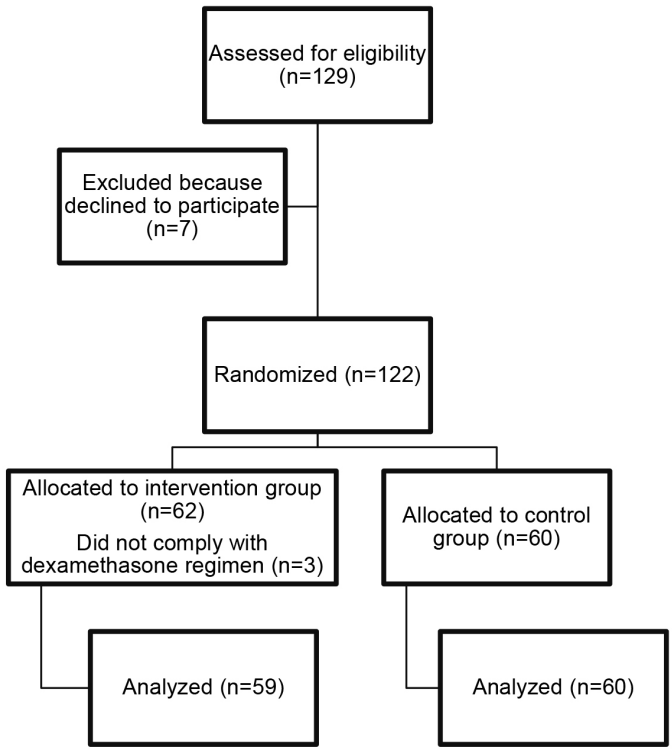

Figure 6. Randomization of patients in Study I.

Table 4. Descriptive statistics of 119 patients with a facial fracture.

	DX+	DX-	P-value
Number of patients	59	60	0.704
Age (median and range)	37 (18.3-82)	40.8 (18.1-72)	0.459
Gender			
Male	46	50	
Female	13	10	
Site of surgery			0.964
ZC	25	26	
Orbital	12	13	
Mandible	22	21	
Surgical approach			0.765
Extraoral	23	25	
Intraoral or combined	36	35	
Duration of anesthesia (min)	92 (49-193)	100 (51-200)	0.365
Postoperative administration of opioids	45	51	0.228

ZC = zygomatic complex

DX+= study group; DX-= control group

Table 5. Descriptive statistics by site of fracture.

	ZC	Orbital	Mandible	P-value
Number of patients	51	25	43	
Age (median and range)	43.4 (21.3-82.4)	49.7 (22.5-74.2)	25.5 (18.1-50.9)	<0.001
Gender				<0.001
Male	40	14	42	
Female	11	11	1	
Surgical approach				<0.001
Extraoral	23	50	0	
Intraoral or combined	28	0	43	
Duration of anesthesia (min)	87 (49-193)	96 (64-200)	102 (58-186)	0.09
PONV (n and % of total)	8 (15.7%)	7 (28.0%)	5 (11.6%)	0.211
Postoperative administration of opioids (n and % of total)	35 (68.6%)	21 (84.0%)	40 (93.0%)	0.001

PONV = postoperative nausea and vomiting

ZC=zygomatic complex

6.1.1 Association between dexamethasone and outcome

Dexamethasone was not found to be effective in preventing PONV in the first 24 h after surgery. PONV was more frequent in the control group (20% vs. 13.6%), but the finding was not statistically significant (p=0.348). (Table 6)

6.1.2 Association of secondary predictors with outcome

Of the 20 patients who suffered from PONV, 14 had received opioids before experiencing nausea and/or vomiting (p<0.001), and all of the patients with PONV had received postoperative opioids (p=0.016). Other predictors were not significant. Detailed statistics are shown in Table 6.

Table 6. Association between PONV and predictors.

	PONV	No PONV	% with PONV	P-value
Number of patients	20	99	16.8	
Age (median and range)	37.7 (18.1-82.4)	44.1 (20.6-65.8)		0.175
Gender				0.934
Male	16	80	16.7	
Female	4	19	17.4	
Site of surgery				0.211
ZC	8	42	16.0	
Orbital	7	18	28.0	
Mandible	5	38	11.6	
Surgical approach				0.641
Extraoral	9	39	18.8	
Intraoral or combined	11	60	15.5	
Duration of anesthesia (min)	111 (63-200)	94 (49-186)		0.065
Postoperative administration of opioids	20	0	100	0.016
Dexamethasone				0.348
Yes	8	51	13.6	
No	12	48	20.0	

PONV=postoperative nausea and vomiting

ZC=zygomatic complex

6.2 Dexamethasone in preventing neurosensory disturbance in zygomatic complex fractures (Study II)

The total number of patients treated for ZC fracture was 79. Of these patients, 70 fulfilled the criteria of having preoperative NSD. Six patients were lost to follow-up before day 30. Thus, the final analyses included 64 patients. Thirty-five patients (54.7%) received either 10 mg or 30 mg of perioperative dexamethasone. Descriptive statistics of Study II patients are shown in Table 7.

Table 7. Descriptive statistics of 64 patients with zygomatic fracture and preoperative NSD.

	DX+	DX-	P-value
Number of patients	35	29	
Age (median and range)	43.9 (20.2-82.4)	40.4 (21.3-67.3)	0.861
Gender			0.469
Male	25	23	
Female	10	6	
Fracture type			
No fracture through foramen	8	7	0.904
Fracture, no impression	9	6	0.637
Impression/comminution in foramen	18	16	0.765
Injury mechanism			
Traffic	9	7	0.885
Assault	14	11	0.866
Sports	2	3	0.492
Falling	7	8	0.476
Other	3	0	0.106
Intraoral approach			0.838
Yes	16	14	
No	19	15	
Timespan from accident to surgery (days, median and range)	4 (0-15)	4 (1-18)	0.876

NSD=neurosensory disturbance

IOF=infraorbital foramen

DX+= study group; DX-= control group

6.2.1 Association between dexamethasone and outcome

Dexamethasone was not effective in reducing postoperative NSD in patients with ZC fractures. Of the study group, 58.3% had NSD at 6 months; the corresponding rate in the control group was 66.7%. The difference was not significant (p=0.516). (Table 8)

6.2.2 Association of secondary predictors with outcome

At the one-month follow-up study subjects who did not have a fracture passing through the IOF had less NSD (86.7% vs. 100%, p=0.009). This difference was also seen at the 6-month follow-up (44.4% vs. 66.7%), although the difference was not significant (p=0.219). Other predictors were not significant. Associations between NSD and predictor variables in Study III are shown in Table 8.

Table 8. Association between NSD and predictor variables in 45 ZC fracture patients at 6 months.

	NSD+	NSD-	% of n with NSD	P-value
Total number of patients	28	17	62.2%	
Age (median and range)	41.1 (21.4-82.4)	47.6 (21.3-63.8)		0.337
Gender				0.664
Male	18	12	60.0	
Female	10	5	66.7	
Fracture type (IOF)				
Fracture through IOF	24	12	66,7	
Impression/comminution	19	8	70.4	0.167
No impression/comminution	5	4	55.6	0.645
No fracture through IOF	4	5	44.4	0.219
Injury mechanism				0.974
Assault	10	6	62.5	
Traffic	7	5	58.3	
Falling	7	4	63.6	
Sports	3	1	75.0	
Other	1	1	50.0	
Intraoral approach				0.463
No	13	6	68.4	
Yes	15	11	57.7	
Timespan from accident to surgery (days)	4 (0-15)	4 (2-18)		0.369
Dexamethasone				0.516
Yes	14	10	58.3	
10 mg	7	3	70.0	
30 mg	7	7	50.0	
No	14	7	66.7	

NSD=neurosensory disturbance

IOF=infraorbital foramen

6.3 Dexamethasone in preventing neurosensory disturbance in orbital floor fractures (Study III)

Twenty-seven patients underwent reconstruction of unilateral orbital floor fracture. Three patients refused to participate in the study and a further three were excluded: one for not having pre- or postoperative NSD, one for requiring re-operation, and one for failing to comply with the dexamethasone dosage regimen. Of the 21 patients remaining, three did not complete the required 6-month follow-up. Thus, 18 patients were included in the analysis. Of these patients, 55.6% (n=10) received perioperative dexamethasone. Sixteen (88.9%) of the 18 subjects had preoperative NSD, and two patients were diagnosed with NSD postoperatively. Descriptive statistics of Study III patients are provided in Table 9.

Table 9. Descriptive statistics of 18 patients with orbital floor fracture and NSD of the ION.

	DX+	DX-	P-value
Number of patients	10	8	
Age (median)	50.6	48.4	0.824
Gender			0.999
Male	5	4	
Female	5	4	
Timespan from accident to surgery (days)	5 (4-11)	6 (3-19)	0.525
NSD diagnosed			0.094
Preoperatively	10	6	
Postoperatively	0	2	
Radiological maximal displacement (mm overall, median and range)	8 (4-12)	10 (1-33)	0.190
Radiological maximal displacement (mm nerve, median and range)	4 (0-8)	4 (0-10)	0.618
Zones (maximal)			
1	1	1	
2	4	5	
3	5	2	

NSD=neurosensory disturbance

DX+= study group; DX-= control group

6.3.1 Association between dexamethasone and outcome

Dexamethasone did not reduce NSD in patients with orbital floor fracture. Of patients in the study group, 50% (5/10) had NSD at 6 months compared with 37.5% (3/8) of patients in the control group (p=0.596).

6.3.2 Association of secondary predictors with outcome

Time from trauma to surgery was a significant predictor for NSD (p=0.018). Age, gender, or radiological findings were not significant. Detailed data of predictors and NSD in Study III are shown in Table 10.

Table 10. Association between NSD and predictors at 6 months postoperatively in orbital floor fracture patients.

	NSD+	NSD-	% of n with NSD	P-value
Total number of patients	8	10	44.4%	
Dexamethasone				0.596
Yes	5	5	50.0%	
No	3	5	37.5%	
Age (years)	49.3 (22.8-81.2)	48.8 (23.8-63.0)		0.965
Gender				0.343
Male	3	6	33.3%	
Female	5	4	55.6%	
Timespan from accident to surgery (days, median and range)	10 (5-19)	5 (3-9)		0.018
Radiological maximal displacement (mm overall, median and range)	8 (1-12)	10 (8-33)		0.058
Radiological maximal displacement of the nerve (mm, median and range)	3 (0-10)	4 (0-8)		0.821
Zones (maximal)				0.201
1	2	0	100%	
2	4	5	44.4%	
3	2	5	28.6%	

NSD=neurosensory disturbance

6.4 Dexamethasone in preventing neurosensory disturbance in mandibular fractures (Study IV)

Thirty-four patients were treated for single or double fracture in the dentate part of the mandible and had postoperative NSD. Patients with a fracture passing through the mental foramen (n=1) and patients who failed to attend the 6-month follow-up (n=6) were excluded from the study. A total of 27 patients were included in the analysis. Fractures were categorized as IAN-bearing (fracture in the angle or corpus of the mandible), non-IAN-bearing (symphysis/parasympysis fracture), or a double fracture (some combination of the above). Descriptive statistics for patients in Study IV are shown in Table 11.

Table 11. Descriptive statistics for 27 patients with mandibular fracture and postoperative NSD.

	DX+	DX-	P-value
Number of patients	14	13	
Age (years, median and range)	26.8 (18.3-41.6)	25.5 (18.6-50.9)	0.790
Gender			0.290
Male	14	12	
Female	0	1	
Timespan from trauma to surgery	2 (0-5)	2 (0-5)	0.766
Site of fracture			0.803
IAN-bearing	3	4	
Non-IAN-bearing	7	5	
Double	4	4	
Cause of NSD			
IAN-bearing			0.809
Trauma	2	3	
Surgery	1	1	
Non-IAN-bearing			0.735
Trauma	2	1	
Surgery	5	4	
Double			0.999
Trauma	2	2	
Surgery	2	2	

NSD=neurosensory disturbance
IAN=inferior alveolar nerve
DX+= study group; DX-= control group

6.4.1 Association between dexamethasone and outcome

At the 6-month follow-up there was a trend that patients who received dexamethasone had more NSD, but the finding was not significant (78.6% vs. 46.2%, p=0.081). (Table 12)

6.4.2 Association of secondary predictors with outcome

Other predictors were not significant. Details are shown in Table 12.

Cause of NSD (trauma vs. surgery) varied between different groups. In patients with IAN-bearing fractures, NSD was caused by trauma in 75% of cases, compared with patients with non-IAN-bearing fractures (28.6%); this difference was significant (p=0.048).

However, NSD in non-IAN-bearing fractures that had been caused by surgery healed significantly more often than NSD caused by a fracture in the IAN-bearing part of the mandible (NSD at 6 months 28.6% vs. 83.3%, p=0.017).

Table 12. Association between prolonged NSD and predictors at 6 months postoperatively.

	NSD+	NSD-	% of n	P-value
All	17	10	63.0%	
Age (years)	26.4 (18.6-50.9)	26.3 (18.3-45.8)		0.980
Timespan from trauma to surgery	2 (0-5)	3 (1-5)		0.151
Site of fracture				0.058
IAN-bearing	10	5	66.7%	
Non-IAN-bearing	2	2	50.0%	
Double	5	3	62.5%	
Dexamethasone				0.081
Yes	11	3	78.6%	
No	6	7	46.2%	

NSD=neurosensory disturbance
IAN=inferior alveolar nerve

7 DISCUSSION

The aim of this study was to clarify the usefulness of perioperatively administered dexamethasone in patients undergoing facial fracture surgery. Specific aims were to investigate whether dexamethasone has an effect in reducing PONV and NSD.

7.1 Methodological considerations

7.1.1 Clinical assessments

PONV and NSD are subjective experiences of patients and therefore somewhat challenging to assess clinically. Comparing subtle differences of particularly PONV between patients is virtually impossible. In the analyses, we therefore chose to categorize sensation as "normal" or "abnormal" and PONV as "no PONV" and "PONV" to have a binary outcome variable.

7.1.2 Postoperative nausea and vomiting (Study I)

A total of 129 patients were eligible for the study during the recruitment period, 122 agreed to participate, and three had to be excluded from the final analysis because of failure to complete all scheduled dexamethasone doses. Thus, a total of 119 patients were included in the final analyses (Study I).

We performed a power analysis retrospectively to evaluate the reliability of our results. With the slightly unbalanced design (59 patients in the dexamethasone group and 60 patients in the control group) and the PONV rates observed (13.6% and 20%, respectively), we estimated a power of 0.66, which is somewhat below the commonly used standard ($0.80 \leq 1\text{-}\beta \leq 0.95$). To achieve the recommended level, a sample size of 81 patients per group would have been optimal.

This study did not control for smoking, history of PONV, or motion sickness. As these are considered risk factors for PONV [85] and perhaps in the case of smoking also for NSD, this can be perceived as a limitation of the study.

The control group did not receive placebo in this study. This decision was made mostly out of necessity. Patients in this study were operated on during the first days after admission to hospital, some even within a few hours of being recruited to the study. Also patients were operated on in two different hospitals with alternating supporting staff over a broad timespan. These circumstances would have made using placebo very challenging and expensive to arrange. There is always a risk for bias when not using placebo, but in this study the risk can be estimated to be

relatively low, as the benefit of GCs in preventing PONV is not very well understood in the general population.

7.1.3 Neurosensory disturbance (Studies II-IV)

The patients included in the analyses of the effect of dexamethasone in reducing NSD (Studies II-IV) were extracted from the randomized patient cohorts. Inclusion criteria were that patients had postoperative NSD, either caused by trauma or surgery, and a follow-up of at least 1 (Study II) or 6 (Studies III, IV) months. In order to achieve groups as homogeneous as possible, we chose to analyze zygomatic, orbital, and mandibular fractures separately.

The final analysis included 64 patients with zygomatic fracture (Study II), constituting 91.4% of the total number of 70 patients identified with NSD. Regarding orbital fractures, 18 patients were included in the analysis (Study III), constituting 78.3% of the total number of 23 patients identified with NSD. Of a total of 34 patients with single or double mandibular fracture in the dentate area, 27 (79.4%) were included in the final analyses (Study IV). The patient material can be considered representative for meaningful analyses. Study populations were not sufficiently large for subgroup analyses.

We performed a power analysis retrospectively to evaluate the reliability of our results.

In Study II with a slightly unbalanced design (n = 24 in the dexamethasone group and n = 21 in the control group) and the rates observed (58.3%/66.7%), we estimated a power of 0.99, which is excellent; the commonly used standard is $0.80<1-\beta<0.95$. To obtain the recommended level of 0.80, a sample size of n = 11 per group would have been sufficient.

In Study III with a slightly unbalanced design (n = 10 in the dexamethasone group and n = 8 in the control group) and the rates observed (50.0%/37.5%), we estimated a power of 0.18, which is clearly below the commonly used standard ($0.80<1-\beta<0.95$). To obtain the recommended level of 0.80, a sample size of n = 40 per group would have been needed.

In Study IV with a slightly unbalanced design (n = 14 in the dexamethasone group and n = 13 in the control group) and the rates observed (78.6%/46.2%), we estimated a power of 0.09, which is clearly below the commonly used standard ($0.80<1-\beta<0.95$). To obtain the recommended level of 0.80, a sample size of n = 189 per group would have been needed.

In conclusion, in Studies III and IV the power being below the commonly used standards constituted the main limitation of the studies.

7.2 Postoperative nausea and vomiting

7.2.1 Occurrence of postoperative nausea and vomiting

Two recently published studies revealed an overall PONV rate of 24-33% among patients who had undergone different types of oral and maxillofacial surgical procedures. [97,99] In a more detailed analysis of the association between type of surgical procedure and PONV, Laskin et al. [99] observed that particularly orthognathic surgery frequently causes nausea (42%). Also other authors have shown notable rates of PONV (40.8-67%) after orthognathic surgery. [94,95,100]

The literature reveals that facial fracture surgery, compared with orthognathic surgery, causes PONV far more infrequently (12.5-14%). [97,99] The comparative rates observed in the present study (I) were also lower, varying between 13.6% and 20%, depending on whether or not the patient had received dexamethasone. One probable reason for the relatively low PONV rate observed in the present study was that the surgical procedures were straightforward and not prolonged in the great majority of cases because patients eligible for recruitment had to have simple, non-comminuted fractures. Moreover, patients with concomitant fractures in the facial region were excluded. Severe and extensive fractures with subsequent longer duration of anesthesia would likely increase the risk for PONV. [86]

Another possible explanation for the lower rate of PONV after facial fracture surgery than after orthognathic surgery may be different gender profiles. Males outnumber females by far among facial trauma patients, as also observed in the present study; 80.7% of the patients were male. Males are known not to be as prone to PONV, as opposed to especially young women, who are at much greater risk. [85]

A study by Albuquerque et al. [98] found intraoral access to be an independent risk factor for PONV, with an odds ratio of 1.290 (CI 95% 1.290-7.304). In our data, surgical approach was not a significant predictor of PONV. One reason for this might be that our data did not include fractures of the maxilla (Le Fort type 1), and our patients did not therefore require broad incisions in the maxilla. Silva et al. showed that orthognathic patients undergoing surgery of the maxilla are more prone to PONV than patients with operations on the mandible, [94] and the same conclusion was drawn by Dobbeleir et al. [100] This can perhaps be explained by challenges in achieving hemostasis in maxilla surgery due to open cavities in the operation area.

7.2.2 Dexamethasone and postoperative nausea and vomiting

In a randomized double-blinded placebo-controlled study by Jahromi et al. [97], the authors aimed to clarify whether preoperative oral administration of metoclopramide, chlorpromazine, gabapentin, or dexamethasone could reduce

PONV after surgical treatment of maxillofacial fractures. The authors observed that metoclopramide, chlorpromazine, and gabapentin were associated with PONV significantly more infrequently than placebo. However, no significant difference was observed between placebo and a single 5 mg oral dose of dexamethasone one hour before surgery. The present study revealed a slightly lower rate of PONV in patients who had received a total perioperative dose of 10 mg to 30 mg of dexamethasone i.v. and i.m. (13.6%) than in those who had not (20%), but the difference was not statistically significant. Although the dose was higher than the recommended dose of 4-5 mg i.v. in the SAMBA guidelines,[7] the PONV reduction was not significant.

Despite dexamethasone being shown to have an antiemetic effect in various types of procedures,[4,134,136] its PONV-reducing effect in facial fracture patients seems uncertain based on existing scientific evidence. This study did not find evidence to support the routine use of dexamethasone in association with surgery of ZC, orbital floor, or isolated, simple mandibular fractures cannot be recommended.

In the present study, the only significant association with PONV was postoperative administration of opioids. Previously, it has been shown that female patients with a history of nausea and vomiting who had opioid medication during the hospital stay and surgery via intra-oral access had a 96% risk of experiencing PONV after oral and maxillofacial surgery, whereas only 6% of males without a history of nausea and vomiting, with no opioid use, and who had surgery via extra-oral access experienced PONV.[98] These findings highlight several important patient-related factors that should be taken into account when evaluating the risk of PONV and the need for prophylactic antiemetic use.

7.3 Dexamethasone and neurosensory disturbance

Our study showed no positive effect of use of dexamethasone in reducing NSD in patients with orbital floor, ZC, or mandibular fractures. According to our knowledge, there have not been any studies conducted previously that have attempted to clarify the potential benefit of dexamethasone in facial trauma surgery. This limits the possibility to compare our findings with pre-existing data, but at the same time opens new undiscovered territory.

Despite the lack of data on the use of GCs in preventing NSD after facial trauma, multiple studies have investigated the effect of locally or systemically administered GCs in orthognathic surgery, particularly in mandibular osteotomies, to reduce NSD. The results are varying.[164,171-174] A recently published systematic review by de Lima et al.[161] concluded that GCs do not reduce NSD in orthognathic surgery.

The mechanisms of how GCs could reduce prolonged NSD in peripheral neural trauma remain somewhat speculative. Al-bishri et al.[13] showed in 2005 that locally

administered betamethasone could have an effect on nerve recovery in a rat model when the crushed nerve section was enclosed in a silicone tube to mimic the bony canal surrounding IAN. The same effect was not noted in the control group, where the nerve was not covered. Mohammadi et al. [14] came to the same conclusions using dexamethasone.

Dexamethasone has been shown to improve the regeneration of crushed inferior alveolar nerves in rats by inhibiting NF-κB activation, which plays a role in regulation of inflammation and apoptosis. [153] Moreover, topically administered GC may reduce scar formation by decreasing fibroblast activity and accelerate the macrophage-related apoptosis and Wallerian degeneration after neurotmesis and microsurgical suturing. [175] Overall, there is evidence that at least in animal models GCs could accelerate the nerve regeneration process and lead to better outcomes.

One hypothesis behind the above-mentioned findings is that GCs relieve pressure on the nerve by reducing edema and subsequently prevent endogenous ischemia of the nerve tissue. This indicates that the effect would be clearer in areas where the nerve tissue is subject to a potential "compartment syndrome" such as in fractures passing through bony canals. Typical examples in the facial region are fractures situated between the mandibular and mental foramina in the mandible and in fractures involving the floor of the orbit and the infraorbital canal. However, our study did not confirm this hypothesis clinically.

In our patient material, the time from trauma to surgery, and therefore, to the administration of dexamethasone, ranged from 3 to 19 days in the orbital floor fracture cohort and from 0 to 5 days in the mandibular angle cohort. This delay is not present in rat models or in orthognathic surgery, where the administration of a GC is performed at the time of tissue trauma. Neural tissue injury causes inflammation during the first hours and apoptosis and Wallerian degeneration during the first week after injury. [28] An additional injury after this critical healing period could cause severe problems regarding regeneration of the nerve tissue. This could be one explanation for why longer treatment delay showed poorer NSD outcome in our orbital floor fracture study population. We did not observe the same effect in the other fracture types, and regarding mandibular fractures in particular, Halpern et al. [176] came to the same conclusion. They reported in their prospective study of 359 fractures that the timing of surgery (range from 0 to 41 days, mean 4.6 days) did not correlate with prolonged NSD. Despite the use of logistic regression to adjust for confounding factors, it is very difficult to categorize the severity of initial trauma because of the abundance of potential confounding factors.

Radiographs show the dislocation at the time of diagnosis, however, they do not reveal the maximum momentaneous dislocation that occurred during the injury. This can lead to an under- or overestimation of the degree of traction to the nerve, skewing the results. Starch-Jensen et al. [65] and Kloss et al. [67] observed

in their retrospective analyses that operated midfacial fractures showed more NSD during follow-up than non-operated ones.[65,67] This finding is, however, significantly biased; we know that trauma-induced NSD in dislocated midfacial fractures is very common, as shown in Study II, compared with non-dislocated midfacial fractures, which we usually do not surgically treat. Despite the lack of prospective studies, due to methodological limitations in retrospective studies and due to many potential confounding factors, it is probably safe to say that fracture surgery causes trauma to an already traumatized nerve tissue, prolonging the healing process in the majority of cases.

7.4 Clinical perspectives

The prevailing trend in medicine is to reduce unnecessary medication and to avoid needless surgery. Dexamethasone is a powerful GC with many justified indications; however, routine use in PONV prevention in facial trauma surgery does not seem to be one of them. This study is in line with the literature, which has not yet been able to show the efficacy of dexamethasone in reducing NSD in clinical settings.

Regarding PONV prevention, there should be a clear indication for the use of multi-drug preventive means (which include dexamethasone as one component), and each patient's risk for PONV should be individually assessed. Overall, patients with facial trauma do not belong in the high-risk group regarding PONV and the routine use of dexamethasone cannot be recommended in this patient group.

Despite some preliminary positive findings in animal trials, there is no evidence that dexamethasone enhances the recovery of NSD in facial trauma surgery. The nerve damage and the ensuing NSD are generally caused by the initial trauma, and the severity of this injury mainly determines the healing potential of the nerve. The power of this study in the case of orbital floor and mandibular fractures was below the commonly used standards. Larger studies should be conducted to confirm the findings of this study.

7.5 Future aspects

Further studies on PONV in facial fracture patients should be targeted to identifying field-specific (i.e. maxillofacial trauma surgery) risk factors for PONV. This could be achieved by controlling known risk factors and organizing a multicenter study to obtain a larger study population. The main focus should be on targeting patients at risk for PONV, as the patient material in maxillofacial trauma surgery differs significantly from typical PONV risk groups.

Regarding NSD, future studies should focus on identifying injury-specific risk factors for NSD. Prospective studies with longer follow-ups of up to a few years should be conducted to determine the end result of NSD, and patient satisfaction and quality of life should be considered in evaluating the true impact of prolonged NSD.

8 SUMMARY AND CONCLUSIONS

1. The incidence of PONV was 16.8%. Dexamethasone did not reduce PONV in facial trauma patients. PONV was significantly more common in patients who had received postoperative opioids.

2. The occurrence of NSD at 6 months postoperatively in ZC fracture patients was 64.4%. Dexamethasone did not reduce NSD in ZC fracture patients.

3. The occurrence of NSD at 6 months postoperatively in orbital floor fracture patients was 44.4%. Dexamethasone did not reduce NSD in orbital floor fracture patients. Time from trauma to surgery was a significant predictor for prolonged NSD in orbital floor fractures.

4. The occurrence of NSD at 6 months postoperatively in mandibular fracture patients was 63.0%. Dexamethasone did not reduce NSD in mandibular fracture patients. NSD in non-IAN-bearing fractures caused by surgery healed significantly more often than NSD in IAN-bearing fractures caused by trauma.

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