

Corticosteroid and cryotherapy in mandibular third molar surgery

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CORTICOSTEROID AND CRYOTHERAPY IN MANDIBULAR THIRD MOLAR SURGERY

**BY
MARIE KJÆRGAARD LARSEN**

DISSERTATION SUBMITTED 2021



AALBORG UNIVERSITY
DENMARK

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by

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LIST OF PAPERS

The present PhD thesis is based on the following five manuscripts published in peer-reviewed journals including two systematic reviews and three original articles. The papers will be referred to by their roman numerals (I-V):

CORTICOSTEROIDS IN MANDIBULAR THIRD MOLAR SURGERY:

- I. Larsen MK, Kofod T, Christiansen AE, Starch-Jensen T. Different Dosages of Corticosteroid and Routes of Administration in Mandibular Third Molar Surgery: a Systematic Review. *J Oral Maxillofac Res.* 2018;29:9(2):e1.
- II. Larsen MK, Kofod T, Duch K, Starch-Jensen T. Short-term Haematological Parameters Following Surgical Removal of Mandibular Third Molars with Different Doses of Methylprednisolone Compared with Placebo. A Randomized Controlled Trial. *J Oral Maxillofac Res.* 2020;11(2):e3.
- III. Larsen MK, Kofod T, Duch K, Starch-Jensen T. Efficacy of methylprednisolone on pain, trismus and quality of life following surgical removal of mandibular third molars: a double-blind, split-mouth, randomised controlled trial. *Med Oral Patol Oral Cir Bucal.* 2020;24094.

CHRYOTHERAPY IN MANDIBULAR THIRD MOLAR SURGERY:

- IV. Larsen MK, Kofod T, Starch-Jensen T. Therapeutic efficacy of cryotherapy on facial swelling, pain, trismus and quality of life after surgical removal of mandibular third molars: A systematic review. *J Oral Rehabil.* 2019;46:563-573.
- V. Larsen MK, Kofod T, Darvann T, Duch K, Starch-Jensen T. Surgical removal of mandibular third molars with or without the use of cryotherapy. A single-blinded randomised controlled trial. *Clinical and Experimental Research.* Submitted February 2021.

ABBREVIATIONS

3D	Three-dimensional
CI	Confidence interval
GCP	Good Clinical Practice
GEE	Generalised estimating equation analysis
ICP	Iterated Closest Point algorithm
MeSH	Medical subject heading
NSAIDs	Non-steroidal anti-inflammatory drugs
OHIP	Oral health impact profile
QoL	Quality of life
RCT	Randomised controlled trial
ROI	Region of interest
SRM3	Surgical removal of mandibular third molar
T0	Before surgery
T1	One day after surgery
T2	Three days after surgery
T3	Seven days after surgery
T4	One month after surgery
VAS	Visual analogue scale

ENGLISH SUMMARY

The present PhD thesis includes two systematic reviews (paper I and IV) and two randomised controlled trials (RCTs) assessing the use of methylprednisolone and cryotherapy following surgical removal of mandibular third molar (SRM3) (paper II, III and V).

SRM3 is the most frequently performed surgical procedure in dental practice. Pain, restricted mouth opening and facial swelling are well-known and common complications following SRM3. Moreover, patients often experience deterioration in quality of life (QoL) and sick leave due to pain and facial swelling. Prophylactic measures are commonly used to prevent or diminish postoperative sequelae following SRM3. The present PhD thesis evaluates the effect of methylprednisolone and cryotherapy to reduce postoperative discomfort following SRM3.

The purpose of paper I was to test the hypothesis of no difference in pain, restricted mouth opening, facial swelling and QoL with different doses and administration routes of corticosteroids following SRM3. The systematic literature search revealed seven studies fulfilling the inclusion criteria. Meta-analysis was not applicable due to heterogeneity among the included studies. The hypothesis of no difference in pain, restricted mouth opening, facial swelling and QoL with different doses and administration routes of corticosteroids could neither be confirmed nor rejected. It was therefore concluded that there was a lack of RCTs evaluating the effect on pain, restricted mouth opening, facial swelling and QoL with different doses and administration routes of corticosteroids following SRM3.

The purpose of paper II and III was to test the hypothesis of no difference in pain, restricted mouth opening, QoL and haematological parameters with different doses of methylprednisolone compared with placebo injected into the masseter muscle prior to SRM3. The study was designed as a split-mouth, double-blind RCT. Fifty-two patients were included involving 104 mandibular third molars, which were allocated to one of the following groups:

- Placebo
- 20mg methylprednisolone

- 30mg methylprednisolone
- 40mg methylprednisolone

Pain, restricted mouth opening, QoL and haematological parameters were assessed after one day, three days, seven days and one month, respectively. No significant difference in pain, restricted mouth opening, QoL and haematological parameters was revealed between different doses of methylprednisolone compared with placebo. It was therefore concluded that a single dose of methylprednisolone prior to SRM3 does not reduce postoperative discomfort. Further studies assessing higher doses of methylprednisolone or other varieties of corticosteroids as well as alternative administration routes are needed before definitive conclusions can be provided about the effect of corticosteroids to diminish discomfort following SRM3.

Paper IV intended to test the hypothesis of no difference in pain, restricted mouth opening, facial swelling and QoL with or without cryotherapy following SRM3. The systematic literature search revealed six studies fulfilling the inclusion criteria. Meta-analysis could not be performed due to heterogeneity among the included studies. The hypothesis of no difference in pain, restricted mouth opening, facial swelling and QoL with or without cryotherapy could neither be confirmed nor rejected. It was therefore concluded that further studies are needed before evidence-based recommendations can be provided about the effect of cryotherapy to diminish postoperative discomfort and improve QoL following SRM3.

The purpose of paper V was to test the hypothesis of no difference in pain, restricted mouth opening, facial swelling and QoL following SRM3 with 30 minutes of continuous cryotherapy compared with no cryotherapy in a single-blinded, split-mouth RCT. A total of 31 patients involving 62 mandibular third molars were included and allocated to 30 minutes of postsurgical cryotherapy or no cryotherapy. Pain, restricted mouth opening, facial swelling and QoL were assessed after one day, three days, seven days and one month, respectively. No significant difference in pain, restricted mouth opening, facial swelling and QoL was revealed between cryotherapy and no cryotherapy. It was therefore concluded that 30 minutes of immediate continuous cryotherapy following SRM3 does not reduce discomfort compared with no cryotherapy. Further studies assessing longer duration of cryotherapy or alternative

application methods are needed before definitive conclusions can be provided about the effect of cryotherapy to diminish postoperative discomfort following SRM3.

The conclusions of the present PhD thesis indicate that methylprednisolone and cryotherapy does not diminish postoperative discomfort or improve QoL following SRM3. However, further studies involving higher doses, other varieties of corticosteroids or administration routes as well as longer duration of cryotherapy or alternative application methods following SRM3 are needed before definitive evidence-based clinical implications can be recommended about these prophylactic measures.

DANSK RESUME

Nærværende ph.d.-afhandling involverer to systematiske oversigtsartikler (artikel I og IV) samt to randomiserede kontrollerede undersøgelser omhandlende anvendelsen af methylprednisolon og kryoterapi i forbindelse med kirurgisk fjernelse af visdomstænder i underkæben (artikel II, III og V).

Fjernelse af visdomstænder i underkæben er den kirurgiske procedure, som foretages hyppigst i tandlægepraksis. Smerte, nedsat gabeevne og hævelse er velkendte komplikationer til kirurgisk fjernelse af visdomstænder. Nedsat livskvalitet og sygemelding opleves ligeledes af mange patienter efter fjernelse af visdomstænder som følge af smerte og hævelse. Forskellige profylaktiske foranstaltninger anvendes derfor ofte med det formål at reducere det postoperative ubehag. Nærværende ph.d.-afhandling har til formål at undersøge, om methylprednisolon og kryoterapi kan nedsætte eller minimere postoperativt ubehag efter kirurgiske fjernelse af visdomstænder i underkæben.

Artikel I havde til formål at teste hypotesen om ingen forskel i smerte, nedsat gabeevne, hævelse og livskvalitet efter kirurgisk fjernelse af visdomstænder i underkæben med forskellige doser og administrationsveje af kortikosteroider. Systematisk litteratursøgning resulterede i syv undersøgelser, der opfyldte inklusionskriterierne. Meta-analyse kunne ikke udarbejdes som følge af heterogenitet mellem de inkluderede undersøgelser. Hypotesen om ingen forskel i smerte, nedsat gabeevne, hævelse og livskvalitet ved forskellige doser og administrationsmåder af kortikosteroider kunne hverken be- eller afkræftes. Det blev derfor konkluderet, at der er behov for yderligere randomiserede kontrollerede undersøgelser, der vurderer effekten på smerte, nedsat gabevene, hævelse og livskvalitet ved anvendelse af forskellige doser og administrationsveje af kortikosteroider i forbindelse med kirurgisk fjernelse af visdomstænder i underkæben.

Artikel II og III havde til formål at teste hypotesen om ingen forskel i smerte, nedsat gabeevne, livskvalitet og hæmatologiske parametre ved anvendelse af forskellige doser methylprednisolon injiceret i musculus masseter sammenlignet med placebo i forbindelse med kirurgisk fjernelse af visdomstænder i underkæben.

Undersøgelsen blev designet som en sideopdelt, dobbeltblindet randomiseret undersøgelse. I alt blev 52 patienter inkluderet involverende 104 visdomstænder i underkæben, som blev allokeret til en af følgende grupper:

- Placebo
- 20mg methylprednisolon
- 30mg methylprednisolon
- 40mg methylprednisolon

Smerte, gabebevne, livskvalitet og hæmatologiske parametre blev vurderet efter henholdsvis en dag, tre dage, syv dage og en måned. Ingen signifikant forskel i smerte, nedsat gabebevne, livskvalitet og hæmatologiske parametre blev fundet mellem de forskellige doser methylprednisolon sammenlignet med placebo. Det blev derfor konkluderet, at en enkelt dosis methylprednisolon før kirurgisk fjernelse af en visdomstand i underkæben ikke antages at reducere det postoperative ubehag. Imidlertid er der behov for supplerende undersøgelser, der anvender højere doser eller andre typer af kortikosteroider og administrationsveje, før der kan anbefales endelige konklusioner om effekten af kortikosteroider til at mindske postoperativt ubehag efter kirurgisk fjernelse visdomstænder i underkæben.

Artikel IV havde til formål at teste hypotesen om ingen forskel i smerte, nedsat gabebevne, hævelse og livskvalitet ved anvendelse af kryoterapi i forbindelse med kirurgisk fjernelse af visdomstænder i underkæben. Systematisk litteratursøgning resulterede i seks undersøgelser som opfyldte inklusionskriterierne. Meta-analyse kunne ikke udarbejdes som følge af heterogenitet mellem de inkluderede undersøgelser. Hypotesen om ingen forskel i smerte, nedsat gabebevne, hævelse og livskvalitet ved anvendelse af kryoterapi kunne hverken be- eller afkræftes. Det blev derfor konkluderet, at der er behov for yderligere undersøgelser, før evidensbaserede anbefalinger kan anbefales om virkningen af kryoterapi til at formindske postoperativt ubehag og bedre livskvaliteten efter kirurgisk fjernelse af visdomstænder i underkæben.

Artikel V havde til formål at teste hypotesen om ingen forskel i smerte, nedsat gabebevne, hævelse og livskvalitet efter kirurgisk fjernelse af visdomstænder i underkæben med 30 minutters postoperativ kryoterapi sammenlignet med ingen

kryoterapi i en enkeltblindet, sideopdelt randomiseret kontrolleret undersøgelse. I alt blev 31 patienter involverende 62 visdomstænder inkluderet og allokeret til 30 minutters kryoterapi eller ingen kryoterapi. Smerte, nedsat gabevene, hævelse og livskvalitet blev vurderet efter henholdsvis en dag, tre dage, syv dage og en måned. Der var ingen signifikant forskel i smerte, nedsat gabevene, hævelse og livskvalitet ved anvendelsen af kryoterapi sammenlignet med ingen kryoterapi. Det blev derfor konkluderet, at 30 minutters kryoterapi efter kirurgisk fjernelse af en visdomstand i underkæben ikke antages at reducere postoperative gener sammenlignet med ingen kryoterapi. Imidlertid er der behov for supplerende undersøgelser, der vurderer effekten af længerevarende kryoterapi eller alternative applikationsmetoder, før kliniske rekommandationer om anvendelsen af kryoterapi til at mindske postoperativt ubehag efter kirurgisk fjernelse af underkæbens visdomstænder kan anbefales.

Konklusionerne i den nuværende ph.d.-afhandling indikerer, at methylprednisolon og kryoterapi ikke mindsker postoperativt ubehag eller forbedrer livskvaliteten efter kirurgisk fjernelse af visdomstænder i underkæben. Imidlertid er der behov for supplerende undersøgelser involverende alternative fabrikater af kortikosteroider, højere doser og administrationsveje samt længere varighed af kryoterapi eller andre applikationsmetoder i forbindelse med kirurgisk fjernelse af visdomstænder i underkæben før evidensbaseret kliniske retningslinjer kan anbefales.

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BACKGROUND

Surgical removal of mandibular third molar (SRM3) is the most commonly performed surgical intervention in dental clinics. The surgical procedure causes injury to the surrounding tissues, which initiates an inflammatory response causing pain, facial swelling, restricted mouth opening and deterioration in quality of life (QoL). Several prophylactic measures have been described in the literature to prevent or diminish postoperative sequelae following SRM3 including non-steroidal anti-inflammatory drugs (NSAID), paracetamol, antibiotics, corticosteroids, cryotherapy, laser, local compression, platelet-rich fibrin and surgical drains (1–7). Corticosteroids and cryotherapy in combination with analgesics are frequently used to lessen postoperative sequelae following SRM3 (8–10). However, the optimal dose, administration method and duration of treatment are presently unknown.

Severe pain, restricted mouth opening, facial swelling, affected QoL and sick leave are frequently expressed by patients following SRM3, although most of the patients usually return to work after one to three days of sick leave (11–13). Complete recovery without pain, normal facial physiognomy, habitual range of jaw movements as well as eating and speaking ability following SRM3 is usually achieved after four to six weeks (11). However, discomfort and sequelae following SRM3 may severely affect QoL during the early postoperative period and could even discourage patients from seeking further dental treatment (14–18).

Therefore, from a patient's point of view, it will be an advantage, if the inflammatory response following SRM3 could be diminished or minimised by prophylactic measures without compromising the natural wound healing process.

INTRODUCTION

MANDIBULAR THIRD MOLARS

The most common indications for SRM3 are infection, caries, periodontal diseases, orthodontics or prophylactic reasons (12,15). In Denmark, approximately 36,000 mandibular third molars are removed per year by general dental practitioners or oral surgeons.

Position of mandibular third molars differs and the used technique for removal varies from simple extraction to advanced surgical intervention. The position is often classified according to Pell and Gregory system as well as Winters classification (19). The frequency and severity of postoperative complications following SRM3 is generally low including pain, restricted mouth opening, facial swelling, bleeding, neurosensory deficiency, alveolitis, delayed healing, infection and damage to neighbouring teeth (13,20). Age, gender, compromised medical status, smoking, poor oral hygiene, anatomy, length of surgical procedure and experience of the surgeon have been associated with increased risk of complications (20).

SRM3 initiates a long-lasting sequence of healing stages including inflammation, epithelialisation, fibroplasia and remodelling. Initially, a vasoconstriction occurs followed by a vasodilatation mediated by histamine, kinins and prostaglandins (21). The empty tooth socket will be filled with coagulated blood following SRM3. Inflammation occurs during the first week, where white blood cells enter the socket to remove any debris. Afterwards fibroblasts and capillaries growth into the socket (fibroplasia). Migration of the epithelium (epithelialisation) will close the extraction alveolus, while osteoclasts accumulate along the crestal bone. The socket will be filled with large amount of granulation tissue in the second week and osteoid deposition begins along the alveolar bone lining. Complete osteoid healing of the extraction socket usually occurs after four to six months (19). Consequently, the inflammatory reaction during the first weeks following SRM3 involving pain, restricted mouth opening, facial swelling and impaired QoL is a natural consequence of the wound healing process.

CORTICOSTEROID

Corticosteroids are steroid hormones produced in the adrenal cortex of vertebrates or synthetic analogues, which are used in a variety of conditions ranging from traumatic brain injuries to skin diseases (22). Corticosteroids exert an anti-inflammatory function including a reduction in vascular dilatation, liquid transudation and oedema formation. Corticosteroids inhibit mast cell production and secretion of cytokine, kinin and histamine, which facilitates a reduction in dilatation and permeability of blood vessels. Furthermore, corticosteroids inhibit synthesis of prostaglandins causing an analgesic effect (23,24). Corticosteroids are classified according to their duration of action in short, intermediate and long acting (Table 1) (9,22). The effect on the inflammatory response appears to be higher, when corticosteroids are administered prior to the surgical intervention (25). Consequently, preoperative administration of long-lasting corticosteroids seems advisable to diminish the inflammatory response following SRM3.

Corticosteroid	Duration of action	Anti-inflammatory potency	Equivalent dose
Cortisol	Short (<12 hours)	1	20mg
Prednisone	Intermediate (12-36 hours)	4	5mg
Prednisolone		4	5mg
Methylprednisolone		5	4mg
Dexamethasone	Long (>36 hours)	25	0.75mg
Bethamethasone		25	0.75mg

Table 1. Duration of action and anti-inflammatory potency of corticosteroids (8).

Side effects to a single dose of corticosteroids in oral surgery has never previously been described (8,26–31). Potential side effects depend on the intensity and duration of treatment. Side effects are primarily seen in long-term therapy and very rarely in therapies lasting less than five days (32). Contraindications to long-term use of corticosteroids are outlined in Table 2. No studies have previously described contraindications to a single dose or short-term use of corticosteroids (33).

Contraindications:	Relative contraindications:
<ul style="list-style-type: none"> • Active viral or fungal infections • Active or untreated tuberculosis • Active acne vulgaris • Primary glaucoma • Acute psychoses or psychotic tendencies 	<ul style="list-style-type: none"> • Hypertension (related to mineralcorticosteroid activity) • Diabetes mellitus • Osteoporosis • Myasthenia gravis • Active or latent peptic ulcer • Acute or long-lasting infections

Table 2. Contraindications for the use of corticosteroids.

The use of corticosteroids to reduce postoperative sequelae following SRM3 are well-described (10,34–36). Betamethasone, dexamethasone and methylprednisolone are the most frequently used corticosteroids in dentistry (8,26–28,30,37). However, the effect on the inflammatory response is inconsistent due to the use of various doses, types and administration routes (8,26). Various doses of dexamethasone significantly diminish pain, restricted mouth opening and facial swelling independent of the administration route (27–29,37,38). Intramuscular or submucosal administration of 4mg dexamethasone has been compared with placebo disclosing significantly less pain as well as lessened restricted mouth opening and facial swelling (27,28). In addition, intramuscularly and perorally administration of 8mg dexamethasone have revealed similar results (29). Consequently, the effect of dexamethasone on the inflammatory responses seems not to be influenced by the administration route (27–29,37,38). An equivalent dose of dexamethasone significantly diminish restricted mouth opening and facial swelling compared with methylprednisolone following SRM3 (30,39). Dexamethasone seems therefore to be more potent and effective to diminish postoperative sequelae after SRM3 compared with methylprednisolone (30,39). Submucosal administration of 40mg methylprednisolone has been compared with placebo disclosing significantly less facial swelling and restricted mouth opening (40). The results of different doses of methylprednisolone are divergent, and assessment of more than two different doses of corticosteroids has never previously been investigated (41).

Administration of corticosteroid causes a higher level of polymorphonuclear leukocytes in the circulating blood as a result of increased rate of entrance from bone marrow and decreased rate of removal from the vascular compartment. In contrast, the number of lymphocytes, eosinophils, monocytes and basophils decreases after administration of corticosteroids. A single dose of cortisol results in 70% decrease of lymphocytes and 90% decrease of monocytes, occurring four to six hours after treatment and persists for approximately 24 hours (42). Cell numbers then rise 24 to 72 hours after treatment (42). Level of peripheral eosinophils after SRM3 has previously been assessed in one study revealing a 50% reduction in the level of eosinophils, when hydrocortisone was administered compared with placebo (31).

Administration of corticosteroids in conjunction with SRM3 seems to diminish pain, restricted mouth opening and facial swelling. However, the optimal administration route, fabricate and most effective dose are presently unknown.

CRYOTHERAPY

Cryotherapy has been defined as the therapeutic use of cold to reduce the inflammatory responses due to vasoconstriction (43). Cryotherapy can be used continuously or intermittently. Application of an ice pack over the cheek immediately following SRM3 is frequently recommended to diminish postoperative sequelae (18). No side effects or discomfort of cryotherapy has previously been described in the literature (44–46). Application of cryotherapy compared with no cryotherapy in conjunction with SRM3 have only been assessed in few RCTs (44,45,47–50). Thirty minutes of intermittent cryotherapy every 1.5 hours for 48 hours have demonstrated significant less pain and restricted mouth opening compared with no cryotherapy following SRM3 (45). However, no significant difference has been revealed with 24 hours of continuous cryotherapy compared with no cryotherapy (47). Consequently, different application methods, duration of treatment time and therapeutic effect have been reported following SRM3 with or without intermittent or continuous cryotherapy (44–47), which is in accordance with the conclusions of previously published systematic reviews (18,51,52).

In conclusion, application of long-lasting intermittent and continuous cryotherapy seems to diminish pain and facial swelling following SRM3. However, prolonged cryotherapy could be problematic to implement in an everyday life or dental practise. Short-term and immediate application of cryotherapy will therefore be more compatible, but RCTs assessing sequelae following SRM3 with short-term cryotherapy combined with a jaw bra are missing. Moreover, three-dimensional (3D) stereophotography measurements of facial swelling following SRM3 with or without cryotherapy with the use of a cold gel pack and a jaw bra have never previously been conducted.

AIMS

The aims of the present PhD thesis were to evaluate the influence of corticosteroid and cryotherapy on postoperative sequelae following SRM3. The specific aims were:

- To conduct a comprehensive and systematic literature search to identify relevant studies assessing postoperative sequelae following SRM3 in conjunction with administration of corticosteroids.
- To evaluate pain, restricted mouth opening and QoL following a single dose of methylprednisolone in the masseter muscle prior to SRM3 compared with placebo.
- To evaluate the influence of a single dose of methylprednisolone prior to SRM3 on haematological parameters including C-reactive protein and leucocytes.
- To conduct a comprehensive and systematic literature search to identify relevant studies assessing postoperative sequelae following SRM3 in conjunction with cryotherapy.
- To evaluate pain, restricted mouth opening, facial swelling and QoL following SRM3 with 30 minutes of postoperative cryotherapy compared with no cryotherapy.

HYPOTHESES

- No difference in pain, restricted mouth opening, facial swelling and immediate QoL following SRM3 between different doses and administration routes of corticosteroids (I).
- No difference in pain, restricted mouth opening and immediate QoL following SRM3 with different doses of methylprednisolone in the masseter muscle compared with placebo (II).
- No difference in haematological parameters including haemoglobin, C-reactive protein and leucocytes following SRM3 with different doses of methylprednisolone in the masseter muscle compared with placebo, after three days (III).
- No difference in pain, restricted mouth opening, facial swelling and immediate QoL following SRM3 with or without postoperative cryotherapy (IV).
- No difference in pain, restricted mouth opening, facial swelling and immediate QoL following SRM3 with 30 minutes of continuous cryotherapy compared with no cryotherapy (V).

MATERIALS AND METHODS

Paper I

Paper I is a comprehensive systematic review following PRISMA guidelines including RCTs in humans assessing treatment outcome following SRM3 with the use of different doses and/or administration routes of corticosteroids.

Research questions:

The research question was formulated according to PICO.

Outcome measures:

- Pain
- Restricted mouth opening
- Facial swelling
- Patient-reported outcome measures and QoL
- Complications

Search strategy:

A Medline (Pubmed), Embase and Cochrane Library search was conducted. RCTs published in English until 1st December 2017 was included. The search strategy was performed in collaboration with a medical librarian utilised a combination of Medical subject heading (MeSH) and free text terms.

Inclusion criteria:

- RCTs in humans
- A minimum of 20 patients

Exclusion criteria:

- Studies with insufficient description of patient selection, surgical procedure, doses of corticosteroids and administration routes as well as studies including medically compromised patients

- Studies comparing the effect of corticosteroids with other pharmacological therapies or combining corticosteroids with other medications

Paper II and III

The study was designed as a double-blinded, split-mouth RCT assessing different doses of methylprednisolone compared with placebo.

The study was carried out at the Department of Oral and Maxillofacial Surgery, Aalborg University Hospital, Denmark between March 2018 and January 2019. The included patients consisted of a population that were scheduled for SRM3 due orthognathic treatment of a facial deformity or recruited from Aalborg University Hospital's Facebook profile. Inclusion and exclusion criteria are outlined in Table 3.

Inclusion criteria:	Exclusion criteria:
<ul style="list-style-type: none"> • Bilateral symmetrical impacted mandibular third molars. • Indication for removal of mandibular third molars. • Age between 18 and 40 years. 	<ul style="list-style-type: none"> • No indication for removal of mandibular third molars. • Unilateral mandibular third molar. • Infections and inflammatory symptoms in the oral cavity at the time of surgery. • Previous maxillofacial trauma. • Craniofacial clefts or syndromes. • Systemic bone disease (i.e. arthritis) or diabetes mellitus. • Active acne vulgaris, viral and fungal infections. • Psychological disease. • Failure to attend follow-up.

Table 3. Inclusion and exclusion criteria for enrolment in paper II and III.

The mandibular third molars were randomly allocated into one of the four groups:

- I: Placebo (isotonic saline solution)
- II: 20mg methylprednisolone
- III: 30mg methylprednisolone
- IV: 40mg methylprednisolone

A computer-aided randomisation scheme was fabricated by the pharmacy including randomisation number and allocation group for each mandibular third molar. A trained assistant nurse received the allocation groups and prepared syringes containing the different mixture of isotonic saline solution and doses of methylprednisolone. All syringes contained 1.05mL of clear liquid. The randomisation sheet was kept exclusively at the pharmacy at Aalborg University

Hospital until the study was unblinded. The patients, surgeon, dental assistant and assessor were blindfolded regarding the allocation group and solution of syringes.

Methylprednisolone was used in the present study instead of dexamethasone or other corticosteroids, as methylprednisolone is the only buyable corticosteroid in Denmark for intramuscular injection following SRM3.

Paper IV

Paper IV is a comprehensive systematic review following PRISMA guidelines including RCTs in humans assessing treatment outcome following SRM3 with or without cryotherapy.

Research questions:

The research question was formulated according to PICO.

Outcome measures:

- Pain
- Restricted mouth opening
- Facial swelling
- Patient-reported outcome measures and QoL
- Complications

Search strategy:

A Medline (Pubmed), Embase and Cochrane Library search was conducted supplemented by a thorough hand-search page by page of relevant journals. RCTs published in English until 17th of July 2018 were included. The search strategy was performed in collaboration with a medical librarian utilised a combination of MeSH and free text terms.

Inclusion criteria:

- RCTs in humans
- A minimum of 12 patients

Exclusion criteria:

- Studies with insufficient description of patient selection and surgical procedure

Paper V

The study was designed as a single-blinded, split-mouth RCT assessing cryotherapy in conjunction with SRM3.

The study was conducted at the Department of Oral and Maxillofacial Surgery, Rigshospitalet, Copenhagen University Hospital, Denmark between March and May 2019. Included patients were scheduled for SRM3 due orthognathic treatment of a facial deformity. Inclusion and exclusion criteria are outlined in Table 4.

Inclusion criteria:	Exclusion criteria:
<ul style="list-style-type: none">• Bilateral symmetrical impacted mandibular third molars.• Indication for removal of mandibular third molars.• Age between 18 and 40 years.	<ul style="list-style-type: none">• No indication for removal of mandibular third molars.• Unilateral mandibular third molar.• Infections and inflammatory symptoms in the oral cavity at the time of surgery.• Previous maxillofacial trauma.• Craniofacial clefts or syndromes.• Systemic bone disease (i.e. arthritis) or diabetes mellitus.• Active acne vulgaris, viral and fungal infections.• Psychological disease.• Failure to attend follow-up.

Table 4. Inclusion and exclusion criteria for enrolment in paper V.

The impacted mandibular third molars were randomly allocated to:

I: No cryotherapy

II: 30 minutes of postoperative continuous cryotherapy with a jaw bra

A computerised random number software (<http://www.randomization.com>, date: 26th December 2018) was used to randomise the mandibular third molars into cryotherapy or no cryotherapy. The software was used to randomly allocate the patients into two groups. Sealed envelopes were used to keep the numbers, and every patient opened one envelope with a specific number. An assistant nurse received the number and combined it with the randomisation sheet to allocate the mandibular third molars into one of the two groups. The randomisation sheet was kept exclusively by

the nurses at the Department of Oral and Maxillofacial Surgery, Rigshospitalet, Copenhagen University Hospital, Denmark, until the study was unblinded.

The surgeon and assessor were blindfolded regarding the postoperative intervention involving cryotherapy or no cryotherapy. The assistant nurse placed a jaw bra with a cold gel pack immediately following SRM3 and removed the jaw bra after 30 minutes, before postoperative precautions were explained to the patients.

ETHICAL CONSIDERATION

Approval to conduct the studies in paper II, III and V were obtained from the Research Ethics Committee and the Danish Data Protection Agency. The studies were performed in accordance with the Declaration of Helsinki II and Consolidated Standards of Reporting Trials (CONSORT) statement (53). In addition, paper II and III was approved by the Danish Health and Medicines Authority and performed in accordance with Good Clinical Practice (GCP).

Potential candidates were given verbal and written information at a clinical visit prior to the surgical procedure. Written informed consent was obtained from every patient before enrolment. Participation was voluntary and patients could at any given time withdraw from the study. The confidentiality of information and anonymity of all patients were respected. Data was stored and analysed in a computer in accordance with guidelines from the Danish Data Protection Agency and GCP. Authors and health personnel involved in the study disclosed any financial or personal relationship with people or organisations that could inappropriately influence their work. The studies did not expose included patients to additional risks compared with standard procedure.

SURGICAL PROCEDURE

Paper II, III and IV

SRM3 was performed in local anaesthesia by the same surgeon (MKL) using a standard technique. All patients received prophylactic analgesics including 400mg ibuprofen and 1,000mg paracetamol, one hour before surgery.

In paper II and III, injection of methylprednisolone or placebo was performed immediately after application of local anaesthesia. The assistant nurse prepared the selected solution of methylprednisolone or placebo without knowledge to the surgeon, dental assistant or patient.

An incision from the anterior border of the ascending ramus of the mandible to the distal part of the lower first molar was performed. The mucosal flap was elevated and the bone around the mandibular third molar was removed with a round burr under irrigation with 0.9% saline solution. If necessary, the mandibular third molar was sectioned with a fissure bur before the tooth was removed. The extraction socket and surrounded bone was irrigated with 0.9% saline solution, and the surgical site was sutured (4-0 Vicryl Rapide®, Ethicon, Johnson and Johnson, Germany).

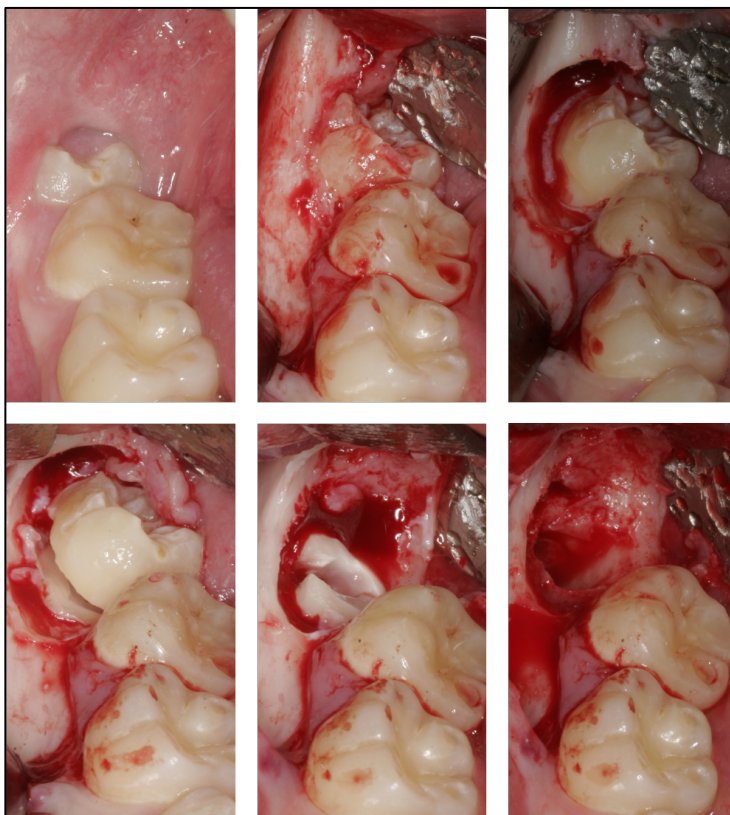


Fig. 1: Clinical photos of the procedure for surgical removal of one mandibular third molar.

In paper V, the assistant nurse placed a jaw bra containing a refreezable, cold gel pack (Soft Stretch Jaw Bra, Cool Jaw, Palmer, US) for 30 minutes following SRM3, if the third molar was allocated to cryotherapy (Fig. 2).



Fig. 2: Clinical photos of a patient wearing a jaw bra.

All patients received standard postoperative instructions including mouth rinse with 0.12% chlorhexidine three times a day, 400mg of ibuprofen three times a day and 1,000mg paracetamol four times a day. Sutures were removed 7 days postoperatively.

OUTCOME MEASURES

Paper II, III and V

Baseline measures were obtained before surgery (T0) and compared with postoperative assessments after one day (T1), three days (T2), seven days (T3) and one month (T4). Following outcome measures were evaluated (Table 5):

Paper II and III:

- Pain
- Restricted mouth opening
- Immediate QoL
- Haematological parameters
- Complications

Paper V:

- Pain
- Restricted mouth opening
- Facial swelling
- Immediate QoL
- Complications

	T0	T1	T2	T3	T4
	Before surgery	1 day postoperative	3 days postoperative	7 days postoperative	One month postoperative
Pain	X	X	X	X	X
Restricted mouth opening	X		X	X	X
Facial swelling	X		X	X	X
Quality of life	X			X	X
Haematological parameters	X		X		
Complications	X		X	X	X

Table 5. Outcome measures and time plan.

Pain

Pain was evaluated using a visual analogue scale (VAS) obtained preoperatively (T0) and compared with postoperative measurements at T1, T2, T3 and T4. Patients were carefully instructed in the use of a 100-mm VAS scale with 0 indicating no pain and 100 indicating worst imaginable pain. Patients marked on a line the point that they felt represented their pain level. VAS score was measured to the nearest mm using a ruler from left to the point marked by the patient.

Restricted mouth opening

Restricted mouth opening was measured as the maximum distance (mm) between upper and lower incisal edges. Baseline measurements were obtained preoperatively (T0) and compared with postoperative measurements at T2, T3 and T4.

Facial swelling

The facial morphology was delineated using a 3D optical scan (David SLS-3 3D scanner, DAVID Vision Systems, Germany) obtained preoperatively (T0) and compared with postoperative measurements at T2 and T3. Patients were positioned one meter from the 3D optical scanner in an upright chair with closed mouth, relaxed facial expression and adequate head support. The position of the 3D optical scanner and the chair was secured in a uniform position valid for all scans. Straight laser

lighters were used to standardise the location of the head in a uniform and reproducible position. The laser line followed the frankfurter horizontal plane (Fig. 3).

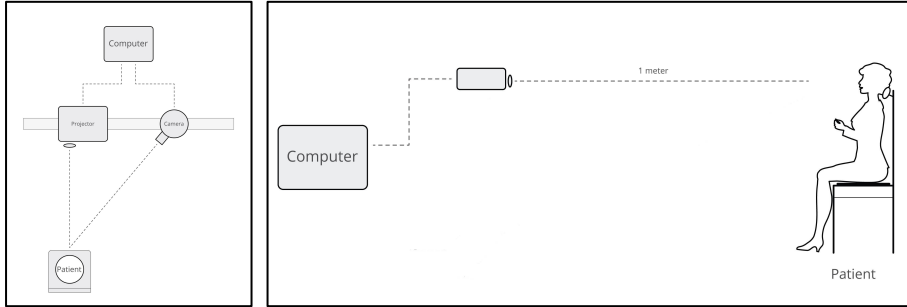


Fig. 3. Illustration of computer, 3D scanner (projector and camera) and patient.

DAVID-4-PRO software (DAVID Vision Systems, Germany) was used to capture the 3D optical scans and convert the scans to STL-files, which were transferred to Landmarker (Software, Landmarker 2.0.6, Denmark) (54). The volumetric difference in the facial morphology between T0 was compared with T2 and T3 using Landmarker and template matching technique (55–57). A recent contribution applying a similar philosophy to calculate facial volume has recently been published (58).

The volume V_s of facial swelling was defined as the volume (in cm^3) of the 3D space located between two face surfaces within a swelling region s . The region of facial swelling was defined as a user-defined region of interest (ROI) in the face, where V_s was to be calculated. The method was devised in such a way that V_s could be monitored in the same swelling region over time and in every subject. A swelling region on an artificially created 3D template face was drawn and the template was subsequently deformed to the shape of each scan, thereby transferring the swelling region to each scan (Fig. 4). This process assured that a portion of a subject scan corresponding to the swelling region would have detailed point correspondence with the swelling region of all other subject scans.

An outline of the swelling region was drawn on the template face surface (Fig. 4a-b), and six anatomical landmarks (Fig. 4a) visible on both the template face surface and the T_0 surface were selected and pointed out by the assessor on both the template surface and the T_0 surface. A sub-region $T_{0,sub}$ of the T_0 surface, which was not expected to be affected by the treatment (a region where only minimal change would occur over time) was selected at the forehead and bridge of nose. The Iterated Closest

Point algorithm (ICP) was used to spatially align all subsequent scans in the same subject, T_i , to $T_{0,sub}$ (59). A similarity transform was applied using the six landmarks obtained to bring the swelling region $S_{template}$ in the template to the general location of the swelling regions s_i in the T_0 scan and all subsequent scans (T_i). The $S_{template}$ was further deformed to each of the s_i regions by moving each point in $S_{template}$ to the closest surface location on s_i . This last step established detailed point correspondence between all the s_i scans. For each triangle in s_i , the distance to the corresponding triangle in s_0 was calculated. A sign was added to the distance depending on whether s_0 was inside (positive sign, swelling) or outside (negative sign, shrinkage) of s_i . The result was a number of m distance maps (an example is shown in Fig. 4c-e). For each triangle in s_0 , a polyhedron (pentahedron, skew triangular prism) with five faces was created by connecting each of its three vertices with the corresponding vertices in s_i , forming a small volume element, and its volume v was calculated (Fig. 4c-d). The volume of the swelling region was the sum of all the volume elements: $V_{si} = \sum(v_j)$, where j counted the triangles in s . Thereby, the volumetric changes in facial morphology were measured.

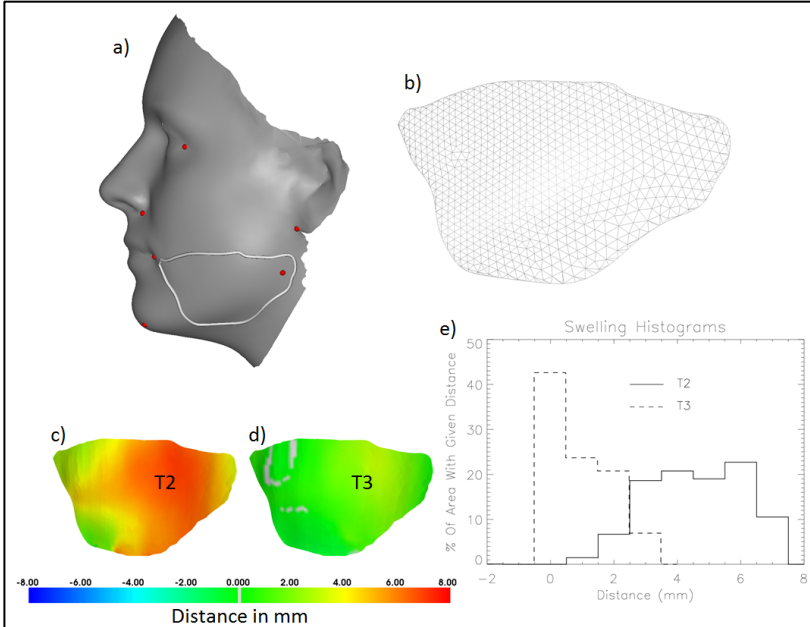


Fig. 4: Illustration of the measurement process of facial swelling. a) The template face scan with the swelling region (white outline) and six alignment landmarks (red spheres). b) Swelling region shown as

wireframe. c) Swelling region in an example subject, colour coded according to distance in mm between surface at T0 and T2. d) Swelling region in the same example subject, colour coded according to distance in mm between surface at T0 and T3. e) Histograms of the distances displayed in figures c) and d). Solid curve: T2, Dashed curve: T3.

The accuracy and precision of the 3D scanner was assessed before the described study was initiated in two pilot studies. A total of 40 scans of a mannequin head were compared with a reference scan of the same mannequin head, which was based on averaging 30 scans of a mannequin head using a 3dMDhead.u (3dMD.com, Atlanta, GA, USA) full head scanner. The distance between the reference and each of the 40 scans was calculated at each surface point after each of the 40 scans had been spatially aligned with the reference using the ICP algorithm (59). Histograms of the distances were created, and corresponding mean and standard deviation of the distances were reported as a measure of accuracy and precision of the David SLS-3 3D scanner. Moreover, 3D scans of eight artificial swellings were compared with reference scans of the same swellings. In order to validate the method of swelling volume calculation, artificial swellings were created by applying silicone material (Coltène President Putty, Coltène Whaledent AG, Switzerland) to the mannequin head. The silicone material was applied in realistic swelling shapes on the mannequin head and scanned in the David SLS-3 3D scanner as well as in a cone beam computed tomography scanner (Planmeca ProMax 3D Max, Planmeca OY, Finland) with voxel resolution 0.4, 0.4, 0.4mm. The silicone material had a different computed tomography value than the mannequin head and could thus be segmented by intensity thresholding. Eight different artificial swellings were created and scanned in both devices and volumes were calculated and compared. In order to determine the threshold parameter for the cone beam computed tomography segmentation, an object of known dimensions (a Lego Duplo brick, The Lego Group, Denmark) (Fig. 5a) was covered in silicone material and scanned in the cone beam computed tomography scanner. The silicone material was segmented in the resulting images using different intensity thresholds, each time measuring the inside width of the silicone shape corresponding exactly to the width of the Duplo brick. The optimal threshold was determined by linear regression in a plot of threshold versus measured width (Fig. 5b).

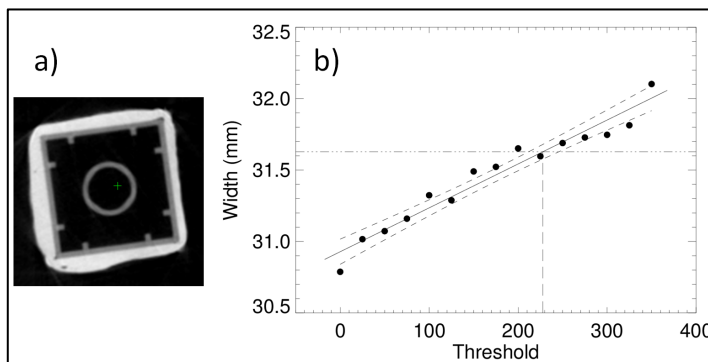


Fig. 5: Determination of optimal cone beam computer tomography intensity threshold for segmentation of silicone material. a) Image slice through cone beam computer tomography scan of a Lego Duplo brick covered with silicone material. b) Plot of the inside width of silicone material encapsulating the Lego Duplo brick as a function of cone beam computer tomography intensity threshold. Solid line is regression line through the points shown. Dash-dotted line indicates actual width of the Lego Duplo brick as measured by callipers.

Quality of life

Immediate QoL was evaluated by oral health impact profile-14 (OHIP-14). Instructions for completing OHIP-14 were explained before patients completed OHIP-14 by themselves, to prevent being influenced by the assessor's opinions and wills. OHIP-14 was filled-out before surgery (T0) and compared with OHIP-14 at T3 and T4. The response format of OHIP-14 was as follows: All the time=4; Very often=3; Fairly often=2; Sometimes=1; Never=0. The OHIP-14 score was calculated as a sum of all 14 questions ranging from 0 to 56, with higher scores indicating poorer oral health related QoL.

Haematological parameters

Blood samples were obtained by a medical laboratory technologist at Aalborg University Hospital, Denmark. Blood samples were collected from the patients before (T0) and three days (T1) after SRM3 with no regard to time of the day, physical activity or fasting. A total of 8mL of whole blood was collected from the cubital vein. Complete haemogram test of the blood samples was conducted within two hours.

Level of haemoglobin (mmol/L), leucocytes (counts x 10⁹/L), neutrophils (counts x 10⁹/L), eosinophils (counts x 10⁹/L) and C-reactive protein (counts/L) were analysed.

Surgical and postoperative complications

Complications were registered at T0, T2, T3 and T4.

STATISTICAL ANALYSIS

Paper I and IV

No meta-analyses could be performed due to considerably heterogeneity among the included studies i.e., different study designs, observation periods, outcome measures, types of corticosteroids and type and duration of cryotherapy.

Paper II, III and V

Power calculation

To ensure adequate power (paper II, III and V), a sample size was made using ClinCalc.com (<http://clincalc.com/stats/samplesize.aspx>, assessed 9th March 2017). The sample size was determined by pain assessment using an expected difference of 20mm in VAS score between placebo and treatment on the first postoperative day with a statistical power of 0.80 and an alpha value of 0.05. Based on sample size calculation and to compensate for possible dropouts and covariates, the sample size was increased to 26 and 31 mandibular third molars in paper II, III and V.

Analyses of results

Data management and statistical analyses were performed using Excel (version 2013, Microsoft, Redmond, Washington, USA) and R (version 3.6.1, Missouri, USA).

Anatomical positions of mandibular third molars were presented as counts and percentage on each treatment group. The time of surgery was presented with mean, standard deviation, minimum and maximum.

Mean difference in pain, restricted mouth opening, facial swelling, QoL and haematological parameters were analysed with a generalised estimating equation

analysis (GEE analysis) for repeated observations. Missing observations in outcome variables were assumed to be missing randomly. The estimated mean value for pain, restricted mouth opening, facial swelling and QoL were expressed with a 95% confidence interval (CI). *P* values of less than 0.05 were considered significant. The analyses were descriptive and adjusted for age, sex, smoking and time of surgery.

RESULTS

The main results of the studies (paper I-V) are presented below.

Paper I

Seven studies fulfilling inclusion and exclusion criteria were included for analysis.

The PRISMA flow diagram presents an overview of the selection process (Fig. 6).

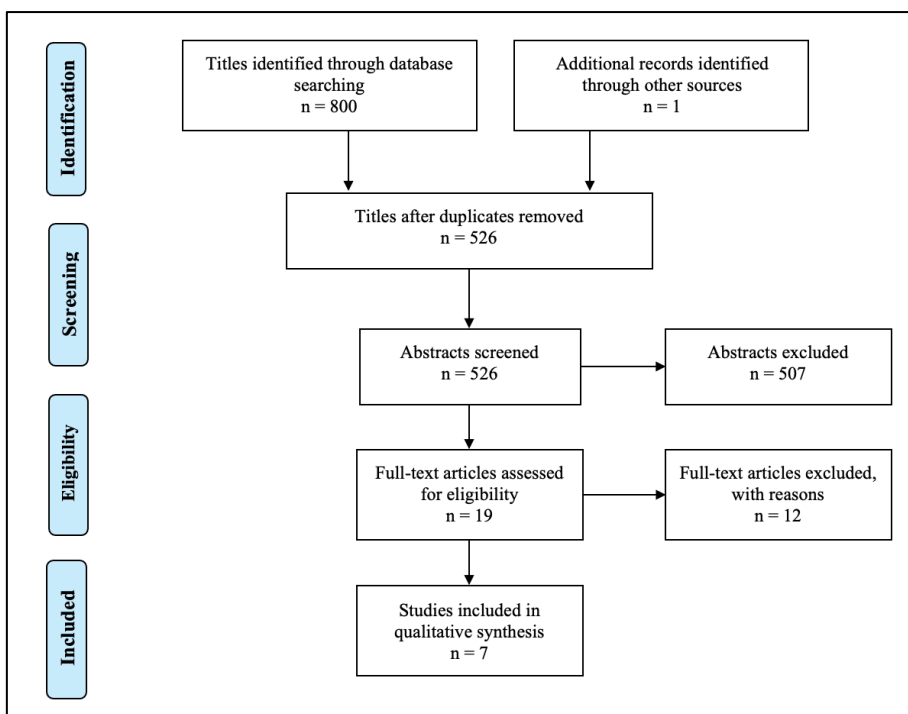


Fig. 6. PRISMA flow diagram demonstrating the results of the systematic literature search.

Different administration routes or doses were assessed in one or four studies (29,40,60–62), while different doses and administration routes of corticosteroids were assessed in two studies (63,64).

The optimal dose and administration route of corticosteroids for diminishing postoperative sequelae after SRM3 could not be clarified.

Paper II and III

Fifty-two patients (16 men and 36 female) with a mean age of 25.9±6 years (range 18-39) were included for statistical analysis. One patient dropped out during the inclusion period and was replaced by another patient. There were no statistically significant differences between the groups with regard to smoking, anatomical position of mandibular third molars and time of surgery (Table 6). The mean surgical time was 9.42 minutes (±5.18). Patients underwent surgical removal of one mandibular third molar, while the other mandibular third molar was removed after 58.8 days (range 8-157). The study was unblinded 13th of May 2019.

Variable	Level	Placebo (n=26)	20mg (n=26)	30mg (n=26)	40mg (n=26)	Total (n=104)
Sex, n (%)	Male	8 (30.8)	8 (30.8)	8 (30.8)	8 (30.8)	32 (30.8)
	Female	18 (69.2)	18 (69.2)	18 (69.2)	18 (69.2)	72 (69.2)
Age, years	mean	24.62	26.81	25.62	26.65	25.92
	(sd)	(4.97)	(6.52)	(6.17)	(6.28)	(5.99)
	median	24.00	25.50	23.00	24.00	24.00
	[Q1, Q3]	[21.00, 26.75]	[22.25, 30.00]	[21.00, 29.00]	[22.25, 30.00]	[21.00, 29.00]
	min max	18.00 38.00	18.00 39.00	18.00 39.00	18.00 39.00	18.00 39.00
Smoking, n (%)	No	24 (92.3)	24 (92.3)	22 (84.6)	24 (92.3)	94 (90.4)
	Yes	2 (7.7)	2 (7.7)	4 (15.4)	2 (7.7)	10 (9.6)
Anatomical position (Winter), n (%)	1	10 (38.5)	8 (30.8)	10 (38.5)	5 (19.2)	33 (31.7)
	2	6 (23.1)	8 (30.8)	4 (15.4)	10 (38.5)	28 (26.9)
	3	5 (19.2)	4 (15.4)	8 (30.8)	6 (23.1)	23 (22.1)
	4	5 (19.2)	6 (23.1)	4 (15.4)	5 (19.2)	20 (19.2)
Anatomical position (P&G transversal), n (%)	1	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.0)
	2	26 (100.0)	24 (92.3)	26	26	102
	3	0 (0.0)	1 (3.8)	(100.0)	(100.0)	(98.1)
				0 (0.0)	0 (0.0)	1 (1.0)
Anatomical position (P&G vertical), n (%)	1	7 (26.9)	5 (19.2)	9 (34.6)	8 (30.8)	29 (27.9)
	2	18 (69.2)	18 (69.2)	16 (61.5)	16 (61.5)	68 (65.4)
	3	1 (3.8)	3 (11.5)	1 (3.8)	2 (7.7)	7 (6.7)
Time of surgery (minutes)	mean	9.27	8.77	9.04	11.73	9.70
	(sd)	(3.79)	(3.90)	(5.87)	(6.77)	(5.30)
	median	9.50	7.00	6.00	9.50	8.00
	[Q1, Q3]	[6.00, 10.00]	[6.00, 10.75]	[5.25, 10.00]	[8.00, 15.75]	[6.00, 11.25]
	min max	5.00 18.00	5.00 20.00	4.00 30.00	4.00 31.00	4.00 31.00

P&G, Pell & Gregory; n, number of wisdom teeth; Q1, first quartile; Q3, third quartile; sd, standard deviation

Table 6. Baseline characteristics, anatomical position of mandibular third molars and time of surgery.

Postoperative instructions were followed by all patients, and none of the patients needed additional prescriptions of analgesics. Facial swelling, discomfort, tenderness and halitosis were reported sporadically. Postoperative bleeding occurred in two patients (1.9%). The bleeding was sufficient treated with supplementary sutures and compression. Twenty-two patients (21.1%) had postoperative antibiotics prescribed due to a combination of major swelling, pus, increased body temperature and sore lymph nodes. Distribution of infection among the four groups was equal with no significant difference ($P=0.676$). None of the patients complained of discomfort or complications related to blood samples. No serious postoperative complications or neurosensory disturbances were observed.

Pain

There were no significant differences in VAS score of pain between different doses of methylprednisolone compared with placebo at any time point (Fig. 7).

A significant higher VAS score of pain was seen in patients with increased age after seven days and one month ($P<0.05$). In addition, males presented a significant higher VAS score of pain compared with females after one month ($P<0.05$).

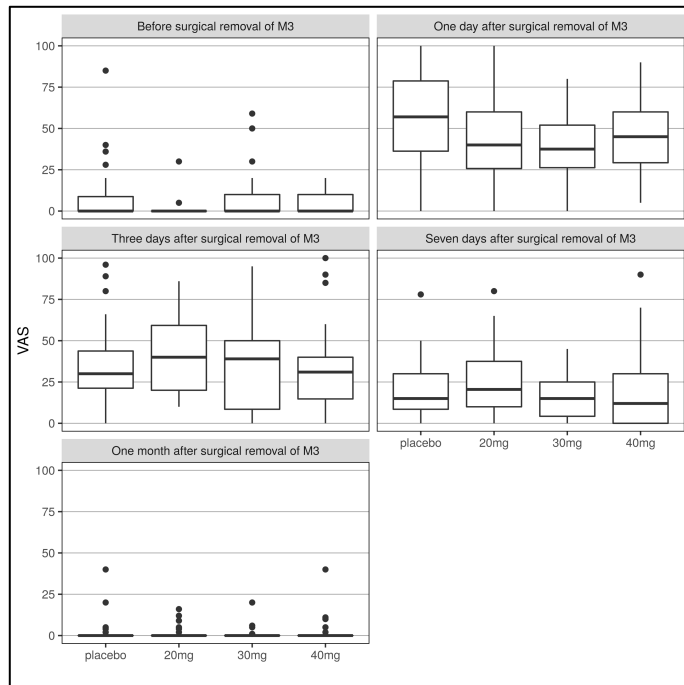


Fig. 7. Boxplot illustrating the variability of VAS score of pain between different doses of methylprednisolone and placebo.

Restricted mouth opening

There were no significant differences in restricted mouth opening between different doses of methylprednisolone compared with placebo at any time point (Fig. 8).

A significant difference was assessed in restricted mouth opening between smokers and non-smokers after three days and seven days ($P<0.05$). A significant difference in restricted mouth opening was seen with an increased time of surgery after three days ($P<0.05$).

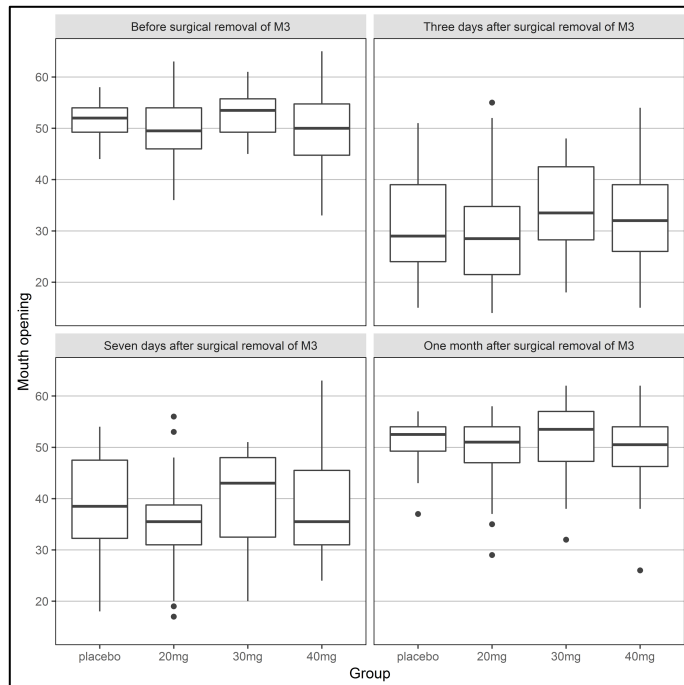


Fig. 8. Boxplot illustrating the variability of restricted mouth opening between different doses of methylprednisolone and placebo.

Quality of life

There were no significant differences in immediate QoL between different doses of methylprednisolone compared with placebo at any time point (Fig. 9). In each group, there were significant differences in the sum of OHIP-14 score between T0 and T3 ($P<0.05$) indicating impaired QoL after seven days.

A significant difference in OHIP-14 score was observed with an increased age after seven days (T3) ($P<0.05$), indicating impaired QoL with increased age.

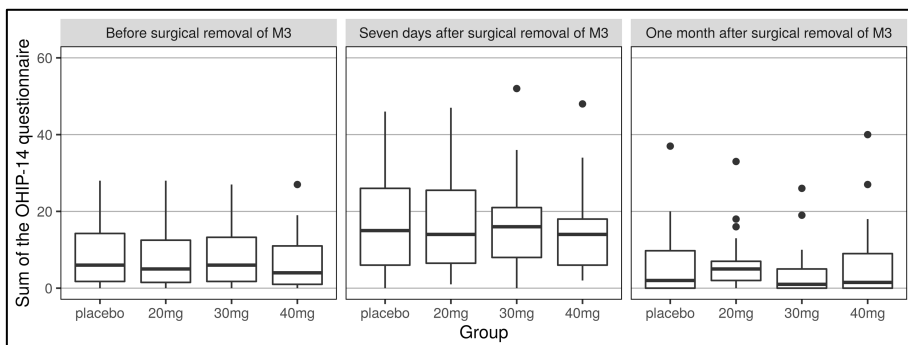


Fig. 9. Boxplot illustrating the variability of OHIP-14 score between different doses of methylprednisolone and placebo.

Haematological parameters

There were no significant differences in the level of haemoglobin between T0 and T1 with different doses of methylprednisolone compared with placebo at any time point (Fig. 10).

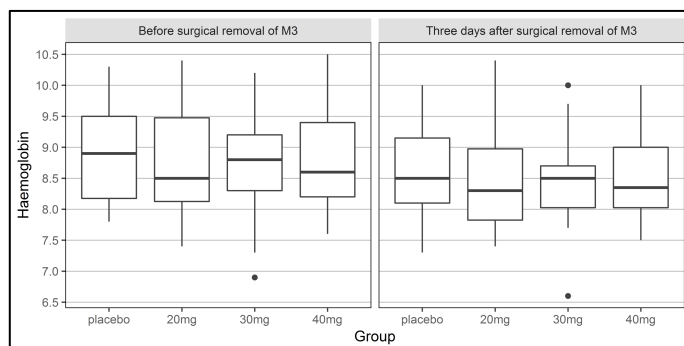


Fig. 10. Boxplot illustrating the variability of haemoglobin (mmol/L) between different doses of methylprednisolone and placebo.

There were no significant differences in the level of total leucocytes, neutrophils and eosinophils between different doses of methylprednisolone compared with placebo at any time point (Fig. 11). The mean level of total leucocytes and neutrophils increased in all groups, whereas the mean level of eosinophils decreased in all groups. A significant difference in the level of eosinophils was seen between T0 and T1, when the results were adjusted for age ($P=0.05$) revealing a larger reduction in level of eosinophils at T1 with increasing age. However, no significant differences in the level

of total leucocytes, neutrophils and eosinophils were seen, when the results were adjusted for sex, smoking and time of surgery.

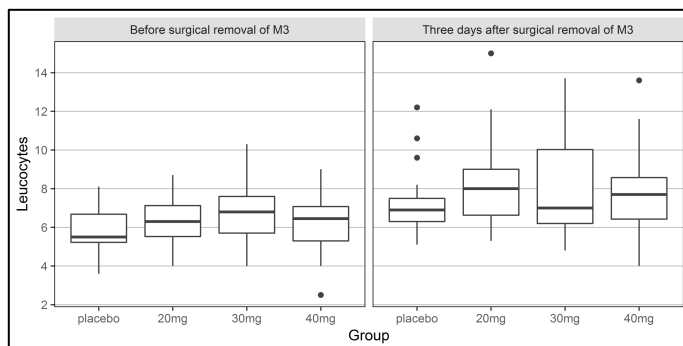


Fig. 11. Boxplot illustrating the variability of leucocytes (counts $\times 10^9/L$) between different doses of methylprednisolone and placebo.

There were no significant differences in the level of C-reactive protein between 20mg methylprednisolone and 40mg methylprednisolone compared with placebo between T0 and T1. However, mean level of C-reactive protein was significantly decreased with 30mg methylprednisolone compared with placebo ($P<0.05$) between T0 and T1 (Fig. 12). A significant difference in the level of C-reactive protein was observed between smokers and non-smokers ($P<0.05$) at T1 indicating that smokers have a lower increase in the level of C-reactive protein compared with non-smokers.

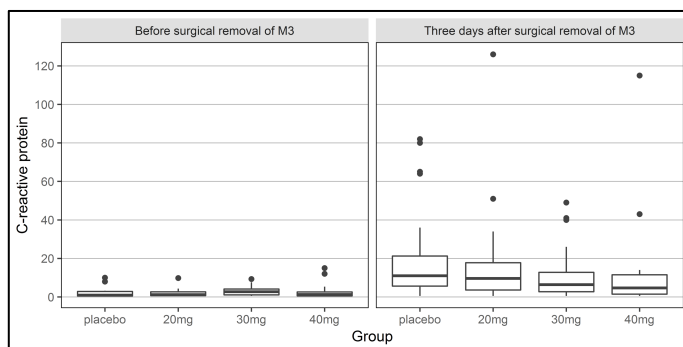


Fig. 12. Boxplot illustrating the variability of C-reactive protein (counts/L) between different doses of methylprednisolone and placebo.

Paper IV

Six RCTs fulfilling the inclusion and exclusion criteria were included for analysis. The PRISMA flow diagram presents an overview of the selection process (Fig. 13).

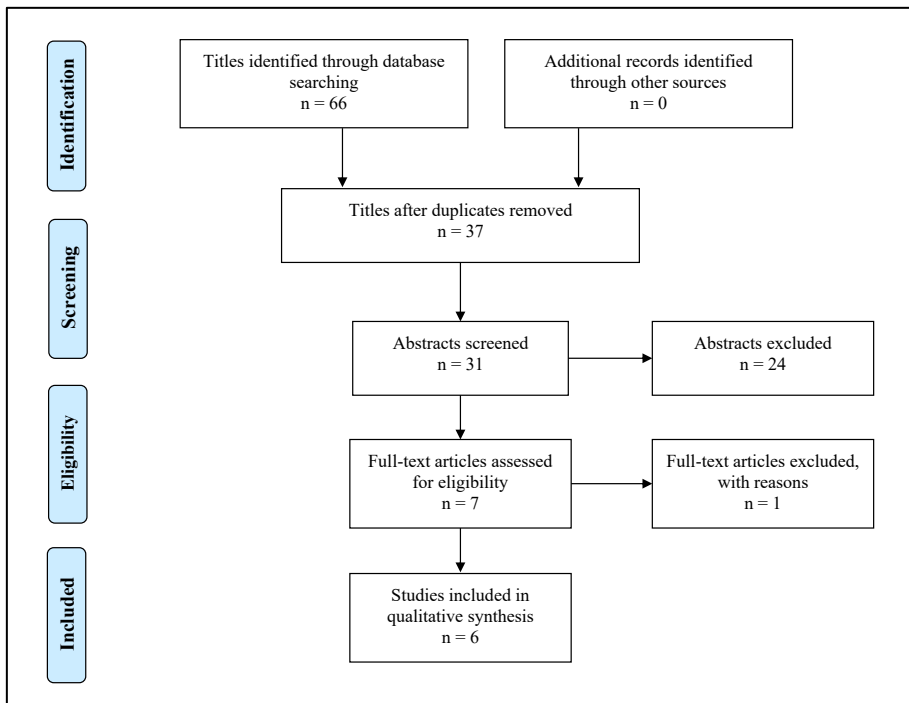


Figure 13. PRISMA flow diagram demonstrating the results of the systematic literature search.

Continuous cryotherapy and intermittent cryotherapy were each assessed in three studies (44,45,48–50,65). Time and device for cryotherapy varied between the studies from 20 minutes to 24 hours.

The optimal application methods and duration of cryotherapy for diminishing postoperative sequelae in mandibular third molar surgery could not be clarified.

Paper V

Thirty-one patients (14 men and 17 female) with a mean age of 22.7 ± 4.6 years (range 18–35) were included for statistical analysis. One patient was lost during follow-up and was replaced by another patient. There were no statistically significant differences between the two groups with regard to smoking, anatomical position of mandibular

third molar and time of surgery (Table 7). The mean surgical time was 7.0 minutes (± 3.7). The study was unblinded 9th of May 2019.

Variable	Level	No cryotherapy (n=31)	Cryotherapy (n=31)	Total (n=62)
Anatomical position (Winter), n (%)	1	20 (64.5)	13 (41.9)	33 (53.2)
	2	5 (16.1)	4 (12.9)	9 (14.5)
	3	4 (12.9)	8 (25.8)	12 (19.4)
	4	2 (6.5)	6 (19.4)	8 (12.9)
Anatomical position (P&G transversal), n (%)	1	0 (0.0)	0 (0.0)	0 (0.0)
	2	29 (93.5)	29 (93.5)	58 (93.5)
	3	2 (6.5)	2 (6.5)	4 (6.5)
Anatomical position (P&G vertical), n (%)	1	10 (32.3)	9 (29.0)	19 (30.6)
	2	13 (41.9)	14 (45.2)	27 (43.5)
	3	8 (25.8)	8 (25.8)	16 (25.8)
Time of surgery (minutes)	mean (sd)	7.39 (4.28)	6.68 (3.05)	7.03 (3.70)
	median	6.00	6.00	6.00
	[Q1, Q3]	[5.00, 9.00]	[5.00, 7.00]	[5.00, 7.75]
	min	3.00	4.00	3.00
	max	20.00	15.00	20.00

P&G, Pell & Gregory; n, number of wisdom teeth; Q1, first quartile; Q3, third quartile; sd, standard deviation

Table 7. Baseline characteristics, anatomical position of mandibular third molars and time of surgery.

Postoperative instructions were followed by all patients. Swelling, discomfort, tenderness and halitosis were reported sporadically. Postoperative antibiotics were prescribed to five patients (6.2%) due to a combination of discomfort, pus, moderate to major swelling, increased body temperature and sore lymph nodes. Additional complications were not observed.

Pain

There were no significant differences in VAS score of pain between cryotherapy and no cryotherapy at any time point (Fig. 14).

However, a significant higher VAS score was seen in males compared with females after one month (T4) ($P < 0.05$).

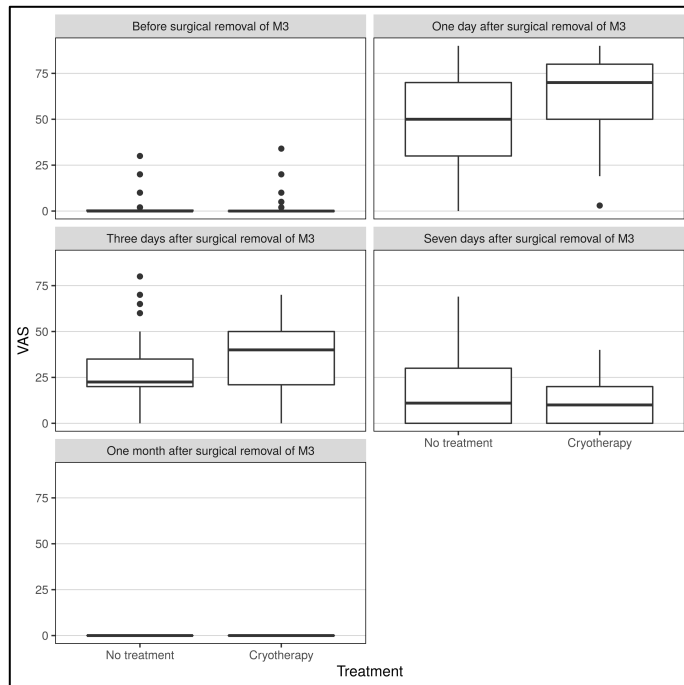


Fig. 14. Boxplot illustrating the variability of VAS score of pain between cryotherapy or no cryotherapy.

Restricted mouth opening

There were no significant differences in restricted mouth opening between cryotherapy and no cryotherapy at any time point (Fig. 15).

A significant decrease in mouth opening was seen with increased time of surgery, after three days (T2) and seven days (T3) ($P < 0.05$).

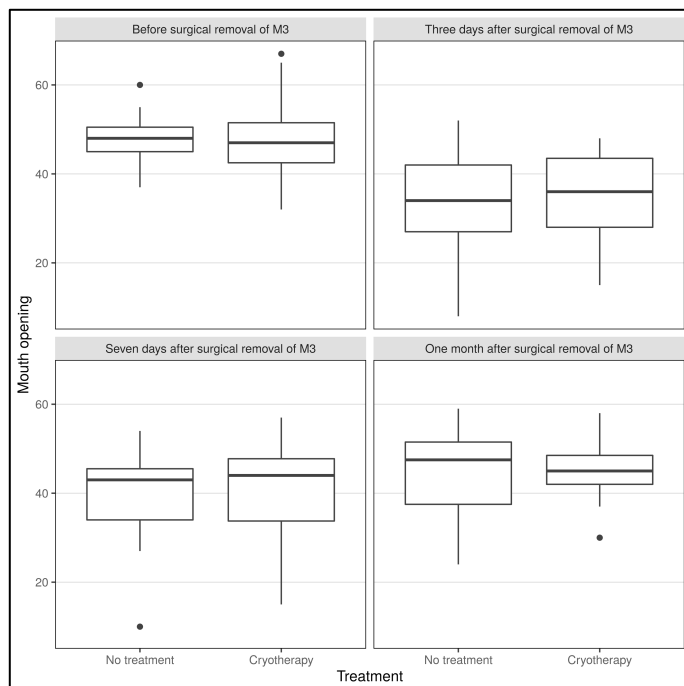


Fig. 15. Boxplot illustrating the variability of mouth opening between cryotherapy and no cryotherapy.

Facial swelling

There were no statistically significant differences between the two treatment modalities at any time point (Fig. 16). However, a tendency to lessened facial swelling was observed with no cryotherapy compared with cryotherapy.

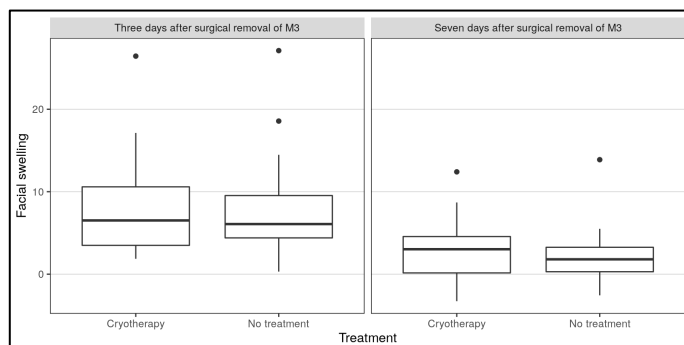


Fig. 16. Boxplot illustrating the variability of facial swelling (cm^3) between cryotherapy and no cryotherapy.

Accuracy and precision of David SLS-3 3D scanner

David SLS-3 3D scanner was highly accurate, reliable and precise during scanning of a static object, when comparing the difference between volumes. The mean and standard deviation of the mean distance histogram was 0.000 ± 0.037 (Fig. 17). The mean and maximum of the differences between volume measurements carried out using the two modalities ($V_{\text{cone beam computer tomography}} - V_{\text{surface}}$) were -0.20 cm^3 and 0.73 cm^3 , ($n=8$), ($P=0.63$), respectively, while the correlation between them was 0.98 (95% CI [0.92;1.00]) (Fig. 18).

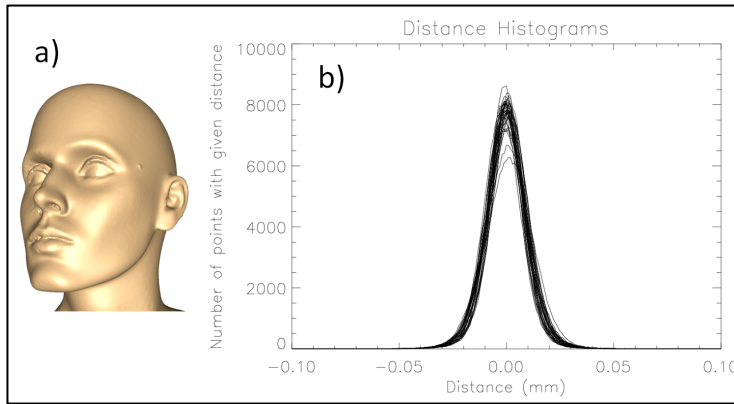


Fig. 17. Validation of the David SLS-3 3D scanner. a) The mean mannequin reference face. b) Histograms of distances between each of the 40 mannequin face surfaces and the reference.

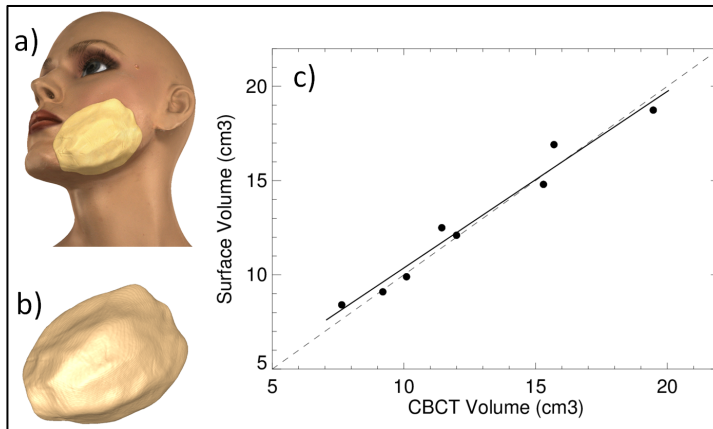


Fig. 18. Validation of swelling volume calculation. a) Mannequin with artificial swelling. b) Segmented swelling from cone beam computer tomography scan. c) Plot of volumes of 8 artificial swellings calculated from cone beam computer tomography (x-axis) and surface scans (y-axis). Solid line is regression line through the 8 points shown; dashed line represents the line of exact correspondence.

Immediate quality of life

There were no statistically significant differences in immediate QoL between cryotherapy and no cryotherapy at any time point (Fig. 19). However, females registered a significantly higher OHIP-14 score compared with males after one month (T4) ($P<0.05$) indicating impaired QoL.

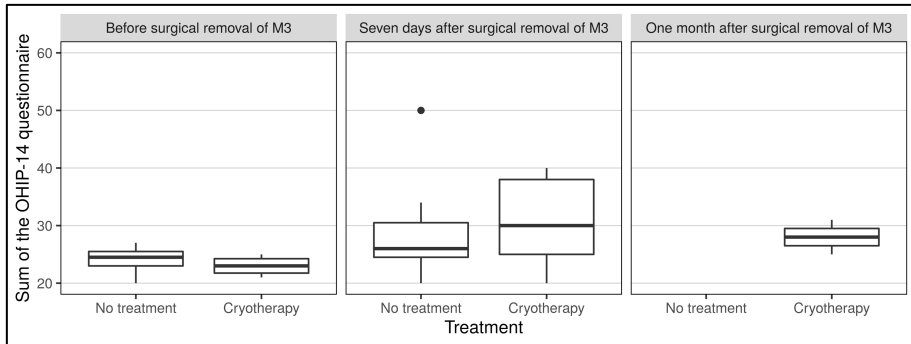


Fig. 19. Boxplot illustrating the variability of OHIP-14 score between cryotherapy and no cryotherapy.

DISCUSSION

The objective of the dissertation was to investigate the influence of different doses of corticosteroids and cryotherapy on postoperative sequelae following SRM3. Two systematic reviews were conducted to clarify the current knowledge about the use of corticosteroid and cryotherapy in mandibular third molar surgery disclosing that the optimal dose of corticosteroid as well as application method and duration of cryotherapy are presently unknown. In an attempt to add new knowledge, two RCTs assessing sequelae following SRM3 with different doses of methylprednisolone or 30 minutes of immediate cryotherapy were conducted.

In the following sections, results of the present RCTs are discussed in relation to pain, restricted mouth opening, facial swelling, QoL and haematological parameters. Finally, methodological considerations and limitations of the studies are emphasised.

PAIN

Pain is an unpleasant sensation induced by noxious stimuli that are sensed by nerve endings of nociceptive neurons (66). VAS, numerical rating and verbal rating scales, faces pain scale-revised, self-administered questionnaires and consumptions of analgesics are frequently used to assess pain score following SRM3 (15,45,48,67,68). VAS, numerical rating scale, verbal rating scale and faces pain scale-revised are considered as valid tools for pain assessment (68,69). However, pain is a subjective and individual sensation, and the overall validity is therefore difficult to assess (69). In generally, patients have different perceptions of pain, which is influenced by various factors such as time of surgery, type and intensity of noxious stimuli, genetics, age, gender, previous dental experience and culture (70–74). Moreover, consumption of anti-inflammatory medications and antibiotics reduce postoperative pain, why inconsistent intake of medication influences the perception of pain score following SRM3 (75,76).

Corticosteroids

Pain relief following administration of corticosteroids is due to an inhibitory effect on prostaglandin formation and diminished facial swelling (77). However, the optimal dose of corticosteroids and administration route for diminishing pain following SRM3 were not clarified in the systematic review (paper I) (41). Moreover, higher doses of corticosteroids seemed not to proportionally diminish pain following SRM3 (41). However, methylprednisolone has demonstrated significantly less pain compared with dexamethasone following SRM3. Though, the dose of methylprednisolone (40mg) was higher than dexamethasone (approximate: 32mg methylprednisolone) (40).

The included studies of the systematic review (paper I) measured pain with VAS. In addition, some of the included studies supplemented VAS score of pain with consumption of analgesics (40,60,62). However, type and dose of analgesics varied among the included studies, which definitely influenced the VAS score of pain and masked the effect of corticosteroids. The optimal study design should therefore include identical consumption of analgesics in order to determine the actual effect of corticosteroids in pain relief.

Paper II revealed no significant differences in VAS score of pain following SRM3 with different doses of methylprednisolone compared with placebo at any time points (78). VAS score of pain was significantly increased with higher age, which is in accordance with previous studies (71,72). Furthermore, males presented with a significant higher VAS score compared with females after one month. Postoperative analgesics were prescribed to all patients, but the actual consumption of analgesics was not recorded. Consequently, the effect of methylprednisolone on pain relief could therefore have been influenced by inconsistent need for analgesics. Further studies assessing higher doses of methylprednisolone or other corticosteroids with identical consumption of analgesics are therefore needed before definitive conclusions can be provided about the beneficial use of corticosteroids in pain relief following SRM3.

Cryotherapy

Pain relief following cryotherapy is due to slowing the conduction of nerve signals (79). However, the optimal application method and duration time for diminishing pain

following SRM3 were not clarified in the systematic review (paper IV) (78). Continuous cryotherapy for 45 minutes and intermittent cryotherapy for 30 minutes in 24 and 48 hours have shown significant less pain compared with no cryotherapy following SRM3 (45,48,49), whereas 24 hours of continuous cryotherapy has shown no significant reduction in pain compared with no cryotherapy (47). Moreover, continuous cryotherapy for 45 minutes with the use of a Hilotherm device has demonstrated significant reduction in VAS score of pain compared with conventional cryotherapy (cool compresses) following SRM3 (80). Consequently, the application methods and duration time seems to influence the therapeutic effect of cryotherapy on pain relief. However, the clinical impact of pain relief must necessarily be adapted to the patient's daily life and dental practice, which is hampered by 48 hours intermittent cryotherapy or regular use of a Hilotherm device following SRM3.

Paper V disclosed no significant differences in VAS score of pain following SRM3 with 30 minutes continuous postoperative cryotherapy on the cheek compared with no cryotherapy (paper V) (81). A jaw bra with a refreezable gel pack were used since it is cheap, easy to adapt to dental practice and does not significantly affect the patient's daily life. However, no beneficial effect on pain relief was achieved. Anti-inflammatory medication inhibits production of prostaglandins and thereby reducing pain and inflammation. Postoperative anti-inflammatory medication (Ibuprofen) was prescribed to all patients, but the actual consumption of anti-inflammatory medication was not recorded. Consequently, the effect of cryotherapy on pain relief could therefore have been influenced by dissimilar consumption of anti-inflammatory medication. Moreover, the use of a jaw bra for a longer period could have improve the effect on pain relief. Further studies assessing the therapeutic effect of cryotherapy should therefore include different time periods with identical consumption of analgesics before definitive conclusions can be provided about the beneficial use of cryotherapy in pain relief following SRM3.

RESTRICTED MOUTH OPENING

Restricted mouth opening is a decrease in mouth opening, also known as trismus, which can occur in relation to oral surgery, pain, infection, temporomandibular

disorders, radiotherapy for head or neck cancer, trauma or neoplastic conditions (82). The severity of restricted mouth opening following SRM3 is often related to the surgical difficulty and length of treatment time (83). Highest level of restricted mouth opening following SRM3 is usually observed on the first postoperative day with a subsequently improvement (83). Restricted mouth opening interferes with patients' ability to eat, speak and maintaining oral hygiene (82). Linear measurement of maximal interincisal distance with a ruler or a Vernier calliper is a simple, reliable, reproducible and validated method, which has previously been used for measurements of mouth opening following SRM3 (44,45,49,50,65).

Corticosteroids

Diminished restricted mouth opening following SRM3 with administration of corticosteroids is presumable due to reduced facial swelling and lessened pain (40,64). A previous study has demonstrated that preoperative submucosal injection of 40mg methylprednisolone significantly diminishes restricted mouth opening compared with placebo (67). However, the optimal dose of corticosteroids and administration route for improving mouth opening following SRM3 were not clarified in the systematic review (paper I) (66). Moreover, a higher dose of corticosteroids seems not to proportionally diminish restricted mouth opening (41). The included studies of the systematic review revealed considerably heterogeneity involving different doses and fabricates of corticosteroids, administration routes and observation periods. Consequently, an association between administration of corticosteroids and improved mouth opening following SRM3 could not be clarified.

Paper II revealed no significant differences in restricted mouth opening following SRM3 with different doses of methylprednisolone compared with placebo at any time points (70), which is in agreement with previous studies (60,62). Smokers disclosed significantly increased restricted mouth opening compared with non-smokers after three and seven days, which is in accordance with previous studies (12,84). However, the smoking habit was not categorised and ranged from rarely to more than 20 cigarettes daily, which interferes with the reliability of the present result. Moreover, no significantly difference in mouth opening following SRM3 has previously been reported among smokers compared with non-smokers (85). A significant association

between increased time of surgery and postoperative deterioration of mouth opening was revealed in paper II, which is in accordance with previous studies (12,86). Infection can cause restricted mouth opening following SRM3 (83). Though, there was no correlation between restricted mouth opening and infection in paper II (87). Assessment of restricted mouth opening following SRM3 seems to be influenced by various parameters. Consequently, a uniform and comparable study design is therefore mandatory to be able to assess whether corticosteroids prevent impaired mouth opening following SRM3.

Cryotherapy

Diminished restricted mouth opening following SRM3 with cryotherapy is probably due to decreased facial swelling, tissue oedema and haematoma (79,88,89). The therapeutic effect of cryotherapy depends on the application methods, duration of treatment time, temperature and depth of the subcutaneous fat (79,88,89). However, the optimal application method and duration time of cryotherapy for diminishing restricted mouth opening following SRM3 were not clarified in the systematic review (paper IV) (70). Intermittent cryotherapy for 30 minutes in 24 hours have demonstrated significant diminished restricted mouth opening compared with no cryotherapy following SRM3 (49), whereas continuous cryotherapy for 24 hours have shown no significant difference in restricted mouth opening compared with no cryotherapy (47).

Paper V disclosed no significant differences in restricted mouth opening following SRM3 with 30 minutes continuous postoperative cryotherapy on the cheek compared with no cryotherapy (81). However, the temperature of the refreezable gel pack was not standardised and thickness of the subcutaneous fat varied among the included patients. Moreover, consumption of anti-inflammatory medications was not registered. A considerably homogenous patient sample and study design is therefore required to assess the beneficial effect of cryotherapy on mouth opening following SRM3.

FACIAL SWELLING

Facial swelling following SRM3 is due to the inflammatory response triggered by the surgical trauma and influenced by patients' characteristics, preoperative difficulty index and intraoperative factors (90). Various techniques and methods have previously been used to monitor and measure facial swelling following SRM3 including callipers, registration of reference points and landmarks, verbal and written response scales, ultrasound, photographic techniques and magnetic resonance imaging (91). Insufficient accuracy, sensitivity and reproducibility are well-known limitations of these methods, since two-dimensional assessment of a 3D volumetric alteration are characterised by inadequate facial depth and shape measurements (92,93). However, 3D imaging technique has made it possible to conduct accurate volumetric measurements of soft tissue alteration following SRM3 (92,93).

Modern concepts of 3D scanning technology seem to be a cheap, valid and reliable tool for quantitative analysis of facial morphology as well as assessment of volumetric facial changes over time (94–96). However, the reliability, accuracy and reproducibility of 3D scanning technology for assessment of changes in the facial morphology at different time points are influenced by alignment errors by the observer as well as variations in facial expression or posture of the scanned subjects (97). Moreover, superimposition and measurements of volumetric changes are associated with inaccuracies due to changes in facial expression or head posture.

In paper V, patients were positioned in an identical distance from the 3D optical scanner in an upright chair with closed mouth, relaxed facial expression and adequate head support. Uniform and reproducible natural head position was secured with laser lights to improve the accuracy, reproducibility and reliability of the method. In addition, two pilot studies were conducted to determine the accuracy and precision of the David SLS-3 3D scanner demonstrating that the David SLS-3 3D scanner was highly accurate, precise and reliable. Template matching technique is a simple tool for superimposition of 3D scans and has previously been used for identifying odontological differences of molars and volumetric changes after facial surgery (58,98). The 3D template can subsequently be deformed to the shape of each scan and thereby transferring the ROI, so the 3D template can be used and fit to each 3D scan.

Corticosteroids

Diminished facial swelling following administration of corticosteroids is due to its anti-inflammatory function including a reduction in vascular dilatation, liquid transudation and oedema formation (23,24). Preoperative administration of corticosteroids significantly diminish facial swelling compared with placebo, as documented in paper I (41). However, the optimal dose of corticosteroids and administration route for diminishing facial swelling following SRM3 were not clarified in the systematic review (paper I), since dissimilar fabricate of corticosteroids, doses and administration route were used as well as different observation periods and two-dimensional assessment methods (66). Moreover, administration of corticosteroids was often combined with dissimilar prescription of anti-inflammatory medication, which amplifies the effect on facial swelling and camouflage the precise value of corticosteroids. Further studies assessing the effect of corticosteroids on facial swelling should therefore include 3D scanning technology and identical consumption of anti-inflammatory medication before definitive conclusions can be provided about the beneficial use of corticosteroids on facial swelling following SRM3.

Cryotherapy

Diminished facial swelling following SRM3 with cryotherapy is probably due to a reduction in the inflammatory response caused by a vasoconstriction (88). The therapeutic effect of intermittent cryotherapy on facial swelling following SRM3 seems to be improved compared with continuous cryotherapy, as documented in paper IV (99). However, the beneficial effect of intermittent or continuous cryotherapy on facial swelling compared with placebo could not be verified due to dissimilar application methods, duration of treatment time as well as different observation periods and assessment methods (78). Nevertheless, intermittent cryotherapy for 30 minutes during 24 and 48 hours revealed a significant reduction in facial swelling following SRM3 compared with no cryotherapy as evaluated by two-dimensional techniques (45,49).

Paper V revealed no significant differences in facial swelling following SRM3 with 30 minutes continuous postoperative cryotherapy on the cheek compared with no cryotherapy as evaluated by 3D facial surfaces and template matching technique after three and seven days (81). A refreezable gel pack in combination with a jaw bra was used as cooling device, since it is cheap, practically applicable in dental practice and does not interfere significantly in the patient's daily life. However, no beneficial therapeutic effect on facial swelling was observed with this type of cooling device, as documented in paper V (81). On the contrary, 45 minutes of immediate Hilotherm cryotherapy compared with conventional cooling compresses revealed a significant reduction in facial swelling as evaluated by 3D optical scanner technique, after two and ten days (80). Hilotherm is a water-circulating external device, where the temperature can be held constant during its use, which often is 15°C (74,81), whereas a refreezable gel pack will not have a constant temperature. On the contrary, if the temperature is too low, drainage of lymph nodes and cell metabolism will be hampered, which will cause oedema and increased facial swelling (100). The use of Hilotherm necessitates that the patient stays at the clinic after the treatment, which is inconvenient for the patient and occupies space at the clinic. Thickness of the subcutaneous adipose tissue may also influence the therapeutic effect of cryotherapy (89). The included patients in paper V were not standardised in terms of weight, face thickness and shape, which may have affected the study results (81). Consequently, further studies assessing the therapeutic effect of cryotherapy on facial swelling following SRM3 should therefore include a homogenous patient sample in relation to thickness of the subcutaneous tissue as well as 3D scanning technology and identical consumption of anti-inflammatory medication before definitive conclusions can be provided about the beneficial use of cryotherapy on facial swelling following SRM3. Furthermore, it is advisable that the method can be applied in dental practice and does not interfere significantly with the patient's everyday life.

QUALITY OF LIFE

Oral health-related QoL is defined as a subjective evaluation of the individual's oral health, functional well-being, emotional well-being, expectations and satisfaction

with care and sense of self (101). Oral health-related QoL is influenced by age, gender, occlusion, present dental disease, previous dental experience, socioeconomic status, education, physical pain, psychological discomfort and psychological disability (71,102,103). Numerous validated oral health-related QoL questionnaires assessing illness, independent living, social relationships, physical senses and psychological well-being have previously been used following SRM3 demonstrating a deterioration in QoL (15,28,104). OHIP-14 and OHIP-49 are the most commonly used questionnaires designed to measure impairment of oral health-related QoL. OHIP-14 is organised into seven conceptual dimensions including functional limitation, physical discomfort, psychological discomfort, physical disability, psychological disability, social disability and handicap. However, OHIP states the patient's overall oral impairment and does not take a specific surgical intervention into account.

Corticosteroids

Diminished deterioration in QoL following administration of corticosteroids is probably due to lessen pain, restricted mouth opening and facial swelling (105). Patient-related outcome measures were not reported in any of the included studies in paper I (41). However, corticosteroids seems to improve QoL following SRM3 compared with placebo (15,28).

Paper II revealed no significant differences in immediate QoL as evaluated by OHIP-14 following SRM3 with different doses of methylprednisolone compared with placebo (87). Improved QoL have been reported following submucosal and peroral administration of 40mg prednisolone (approximate: 32mg methylprednisolone) compared with placebo (15). This result contrasts with the present study, which could be due to that antibiotics and ibuprofen were prescribed postoperatively, while ibuprofen and paracetamol were solely prescribed in the present study.

Previous studies have shown a higher deterioration in QoL with increasing age (17,106). In paper II, OHIP-14 score was significantly increased with higher age after seven days. Gender seems not to influence immediate QoL (paper II), although a previous study has reported that females seem to have a higher risk of poor recovery and worsening in immediate QoL following SRM3 compared with males (12). Increased time of surgery is reported to influence QoL (106), which is in contrast to

results of paper II. Further studies assessing the effect of corticosteroids on QoL should therefore be conducted to assess whether corticosteroids prevent deterioration in QoL following SRM3.

Cryotherapy

Less pain, restricted mouth opening and facial swelling are probably the reasons for diminished deterioration in QoL following SRM3 with cryotherapy (105). The therapeutic effect of intermittent and continuous cryotherapy on QoL following SRM3 seems to be improved compared with no cryotherapy, as documented in paper IV (99). Significant less deterioration in QoL was seen with the use of continuous cryotherapy for 45 minutes and 24 hours and intermittent cryotherapy in 30 minutes for 24 hours (48,49,65). Though, different questionnaires were used to assess the effect of cryotherapy on QoL following SRM3 (2,48,49,65,78). Assessment of QoL is recommended to be evaluated by validated and uniform methods or questionnaires to improve the reliability of the results. Consequently, a uniform and comparable study design is thus necessary to be able to assess whether cryotherapy has an impact of QoL following SRM3.

In paper V, OHIP-14 questionnaire revealed no significant differences in QoL between cryotherapy and no cryotherapy at any time point even after the groups were adjusted for age, smoking and length of surgery (81). OHIP-14 evaluates patient's overall oral impairment and does not focus on a specific surgical intervention. Consequently, further RCTs assessing QoL following SRM3 should include additional self-administrated questionnaires focusing on patient's perception of the surgical intervention. Furthermore, self-administrated questionnaires are also recommended to include an association between QoL and demographic factors, socioeconomic status as well as educational background.

Different cooling devices can be used for cryotherapy. The temperature of a refreezable gel pack will rise during use, whereas a Hilotherm device will keep a constant temperature (80,104). The use of Hilotherm device has previously revealed significant improved QoL following SRM3 compared with no cryotherapy as evaluated by a questionnaire (104). However, solely ten patients were included, and the time period varied between 0 to 20 hours per day. Further RCTs evaluating the

effect of cryotherapy in QoL are needed using standardised, validated and evidence-based questionnaires before recommendations and guidelines can be provided.

HAEMATOLOGICAL PARAMETERS

Haematological parameters are influenced by various factors, including age, gender, ethnicity, diet, life-style, medication, anaemia, pregnancy, smoking and intraoperative bleeding (107,108). Prolonged time of surgery may cause a decrease in the level of haemoglobin due to increased blood loss (109). However, SRM3 is usually associated with minor blood loss, though life-threatening haemorrhage has been reported (110).

Corticosteroids

Local or systemic administration of corticosteroid may influence the haematological parameters (42,111). Previous studies have demonstrated that levels of haemoglobin and leucocytes in peripheral blood increase in conjunction to corticosteroid therapy (42,111).

Paper III revealed decreasing levels of haemoglobin and increasing levels of leucocytes and C-reactive protein compared with preoperative blood levels, three days following SRM3 (112). However, no statistically significant difference was observed in the haematological parameters between different doses of methylprednisolone compared with placebo (112). Methylprednisolone has a duration of action of 12-36 hours and a plasma half-life time of 3-4 hours (113). Peripheral blood samples were therefore obtained before SRM3 and after three days, when methylprednisolone's duration of action was ended, and the haematological parameters were anticipated to be normalised. The results of paper III show that a single dose of methylprednisolone does not compromise haematological parameters compared with placebo.

Elderly patients are characterised by lower levels of haemoglobin and leucocytes in peripheral blood (108,113,114). In paper III, there were no significant differences in the level of haemoglobin or leucocytes, when the results were correlated for age. However, patients' age ranged from 18 to 39 years, which might explain the reason for no statistical difference in the haematological parameters. However, pre- and postoperative peripheral blood samples revealed a significantly larger decrease in the

level of eosinophils with increasing age. This result is in accordance with the literature demonstrating that levels of eosinophils decrease with advancing age (115).

Smoking increases the level of haemoglobin, leucocytes and C-reactive protein in peripheral blood compared with non-smoking (116,117). In paper III, there were no significant differences in the level of leucocytes between smokers and non-smokers. However, a significant lower level of haemoglobin and C-reactive protein was observed in smokers compared with non-smokers. These results seem not to be in accordance with previous studies, which may be due to the fact that only five low smokers were included in the present study (116,117). Thus, the influence of smoking on haematological parameters within this study may not be representative.

LIMITATIONS

A systematic review is a meticulous and structured synthesis of empirical evidence that consists of a predefined medical research question. Systematic reviews and meta-analyses are considered as the best evidence for answering a definitive research question due to the transparency of each phase of the synthesis process that delimit bias. Conclusions of a systematic review represent a detailed and comprehensive overview of available evidence on a given topic and therefore frequently used for developing clinical practice guidelines and defining future research agendas. However, the value and strength of a systematic review is compromised by the selection of studies, heterogeneity among the included studies, inappropriate subgroup analyses, publication bias and loss of information on important outcomes due to predefined eligibility inclusion criteria and systematically extraction of specified data. Systematic reviews are frequently combined with a meta-analysis in evidence-based medicine to increase the strength of evidence and improved the statistical power. Meta-analysis is a statistical method that integrates and combine results of comparable studies. However, combining studies in a meta-analysis that differ substantially in design, outcome measures and observation period yield to no meaningful conclusions. The current knowledge of corticosteroid and cryotherapy to diminish postoperative discomfort following SRM3 were assessed in systematic reviews (paper I and IV). Meta-analyses were not conducted due to limited number of studies fulfilling the

inclusion criteria as well as various methodological confounding factors and heterogeneity among the included studies. Hence, conclusions drawn from the results of the systematic reviews should be interpreted with caution.

Assessment of pain, restricted mouth opening, facial swelling and QoL following SRM3 with the use of corticosteroids or cryotherapy are influenced by patients' characteristics, preoperative difficulty index, intraoperative factors, consumption of anti-inflammatory medication as well as the used evaluation methods (85,118). Consequently, paper II, III and V as well as the present dissertation contains considerably bias and various confounding factors, which influence the reliability of the study results. The proposed conclusions and clinical recommendations of the present dissertation should therefore be interpreted with caution due to the small sample size, inclusion of smokers and non-smokers, no systematically registration of consumption of analgesics or the applied temperature of the jaw bra as well as no standardisation according to uniform thickness of the subcutaneous tissue. In addition, socioeconomic status, educational background and level of daily physical activity were not registered, which significantly influence patient's perception of recovery, pain, facial swelling and QoL following SRM3.

Pain was evaluated by VAS, which is a valid and reliable tool for pain assessment. Alternative methods as verbal rating scale and faces pain scale-revised may contain additional information about pain interference and unpleasantness. Furthermore, VAS and OHIP-14 questionnaire were answered with no regard to time of the day or standardised according to time for consumption of analgesics, which could have influenced perception of pain and QoL.

Peripheral blood samples were obtained at dissimilar timepoints with no regard to time of the day, physical activity or fasting, which might have influenced the haematological parameters.

A refreezable gel pack and a jaw bra were used as cryotherapy following SRM3. The temperature of the gel pack as well as the thickness of the subcutaneous tissue were not registered, why the effect of cryotherapy could have been different among the included patients. Moreover, the initial temperature of the cold gel pack might have increased differently, so that the effect of cryotherapy could have been absent in some patients.

CONCLUSION

- The optimal dose and administration route of corticosteroids for diminishing pain, restricted mouth opening, facial swelling and immediate QoL seems to be unknown. Further well-designed RCTs assessing the effect of corticosteroids in conjunction with SRM3 are needed before evidence-based clinical recommendations can be provided.
- A single intramuscular administration of 20-40mg methylprednisolone in conjunction with SRM3 seems not to diminish pain, lessen restricted mouth opening or improve immediate QoL compared with placebo.
- A single intramuscular administration of 20-40mg methylprednisolone does not seem to affect haematological parameters including haemoglobin, leucocytes and C-reactive protein, three days following SRM3.
- There are no evidence-based recommendations for the use of postoperative cryotherapy following SRM3 to diminish pain, lessen restricted mouth opening or facial swelling and improve immediate QoL. Further well-designed RCTs assessing the effect of cryotherapy in conjunction with SRM3 are needed before evidence-based clinical recommendations can be provided.
- The therapeutic effect of 30 minutes cryotherapy following SRM3 to diminish pain, lessen restricted mouth opening or facial swelling and improve immediate QoL seems to be negligible compared with no cryotherapy.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVE

Pain, restricted mouth opening, facial swelling and deterioration of immediate QoL are well-known and common sequelae following SRM3. Prophylactic measurements including corticosteroids and cryotherapy are frequently used to diminish discomfort following SRM3. However, there are no evidence-based recommendations for the beneficial effect of these prophylactic measures including optimal fabricate and dose of corticosteroids, administration route as well as duration of cryotherapy and application method. No beneficial effect of methylprednisolone or short-term continuous cryotherapy on postoperative discomfort following SRM3 was revealed in the present thesis. Consequently, these prophylactic measurements should not be used routinely. However, the present thesis contains various methodological confounding factors as well as bias, which may have influenced the proposed conclusions. Further well-designed RCT assessing the effect of corticosteroids and cryotherapy on pain, restricted mouth opening, facial swelling and QoL following SRM3 should therefore involve a uniform patient sample, identical consumption of analgesics, 3D measurements and validated questionnaires involving socioeconomic status, educational background and level of daily physical activity before evidence-based clinical recommendations can be provided.

Methylprednisolone has an intermediate duration of action. A single dose of methylprednisolone (20-40mg) injected in musculus masseter immediately prior to SRM3 (paper II and III) revealed no beneficial effect on postoperative discomfort compared with placebo following SRM3. Higher doses of methylprednisolone or corticosteroid with long-lasting duration of action could hypothetically have a beneficial effect on pain, restricted mouth opening, facial swelling and QoL. Moreover, prolonged treatment periods or alternative administration routes could tentatively diminish postoperative discomfort. However, these aspects need to be clarified in further studies.

Application of long-term cryotherapy following SRM3 can be unpleasant and interfere with patient's daily life. Thirty minutes of postoperative continuous cryotherapy with a refreezable gel pack in a jaw bra was therefore used in paper V, since it is cheap, practically applicable in dental practice and does not interfere

significantly in the patient's daily life. However, no beneficial effect on postoperative discomfort was observed with the use of short-term cryotherapy following SRM3. Prolonged and/or intermittent cryotherapy as well as alternative application methods or other devices could theoretically have improved the therapeutic effect of cryotherapy. However, the therapeutic effect of cryotherapy is significantly influenced by patients' characteristics, preoperative difficulty index, intraoperative factors including time of surgery and consumption of anti-inflammatory medication. Further studies assessing the therapeutic effect of cryotherapy following SRM3 should therefore include a meticulous homogenous patient sample as well as standardisation of the temperature and application method to minimise bias and various confounding factors.

Facial swelling following SRM3 has previously been assessed mainly by two-dimensional measurements. However, it is problematic to obtain quantitative informations about a 3D facial swelling, based on two-dimensional measurements. A 3D optical scanner and template matching technique was used in paper V for assessment of facial swelling following SRM3 revealing high accuracy and precision. Consequently, further studies assessing facial swelling following SRM3 with the use of corticosteroids or cryotherapy should include 3D measurements.

No beneficial effect of corticosteroids or cryotherapy on postoperative discomfort following SRM3 was revealed in the present dissertation. However, new knowledge, scientific considerations as well as a reliable and high accurate 3D method for assessment of facial swelling was present. Moreover, the dissertation emphasises the importance of uniformity and standardisation in patient characteristics, study design, preoperative difficulty index, assessment methods and observation period as well as analysis of socioeconomic status and educational background is needed to delimit bias and obtain valid results, when assessing the beneficial effect of corticosteroids and cryotherapy on postoperative discomfort following SRM3.

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APPENDIX: PAPER I-V

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