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Non-pharmacological prevention of postoperative complications associated with impacted third molars. Integrative systematic review

Caterina Oliveira Domingues

Dissertação conducente ao Grau de Mestre em Medicina Dentária (Ciclo Integrado)

Gandra, 27 de junho de 2022

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Trabalho realizado sob a Orientação de Mestre José Adriano Costa

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Eu, acima identificado, declaro ter atuado com absoluta integridade na elaboração deste trabalho, confirmo que em todo o trabalho conducente à sua elaboração não recorri a qualquer forma de falsificação de resultados ou à prática de plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria do trabalho intelectual pertencente a outrem, na sua totalidade ou em partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores foram referenciadas ou redigidas com novas palavras, tendo neste caso colocado a citação da fonte bibliográfica.

DEDICATION

It is with special regard and appreciation that I dedicate this dissertation to my closest family members. To my beloved parents, Alda and Alírio, and my siblings, Gabriela and Pedro, who have always been present during these five years and continue to encourage me to follow my dreams. To my wonderful aunts, Miria, Marília and Nelida, who never stopped believing in my potential and support me unconditionally.

I would also like to dedicate this work to someone that truly inspires me, my precious friend and colleague Ryan, who reassured me many times and helped me throughout the entire process. I have no words to adequately express my gratitude.

ACKNOWLEDGEMENTS

The completion of this dissertation would not have been possible without the guidance of an amazing professor and adviser, Dr. José Adriano Costa. Thank you so much for your availability, dedication and especially for believing in my capabilities and pushing me forward to complete something that did not seem possible to me at first.

To Prof. Dr. Paulo Rompante and Prof. Dr. Filomena Salazar, who helped me to clarify some doubts in order to complete this dissertation, I sincerely appreciate your time.

Moreover, I would like to thank the entire institution for giving me the opportunity to learn and develop skills which will allow me to pursue my dream every single day.

RESUMO

Introdução: A cirurgia de terceiros molares impactados é um procedimento comum, contudo, como qualquer procedimento cirúrgico, envolve riscos.

Objetivos: O objetivo desta dissertação é identificar, sistematizar e categorizar os métodos não farmacológicos de prevenção de complicações pós-operatórias associadas à extração de terceiros molares impactados.

Material e métodos: Pesquisa bibliográfica realizada na base de dados PubMed. Os artigos incluídos foram publicados entre 2012 e 2022. Foi utilizado o protocolo PRISMA 2020 e a metodologia PICO.

Resultados: Através da análise dos artigos verificou-se que: cicatrização por segunda intenção reduz edema, dor e trismo; uso de clorexidina minimiza edema, trismo, dor e osteíte alveolar; água ozonizada e destilada são irrigantes comparáveis; PRF reduz edema, trismo, dor, profundidade de sondagem e melhora a cicatrização; retalhos envelope e triangular reduzem edema e trismo, e profundidade de sondagem, respetivamente; ponto contínuo festonado diminui deiscências; a CBTC é mais precisa na previsão da exposição do nervo em comparação com a PAN; vitamina D3 pode reduzir edema e fatores pró-inflamatórios; e a acupuntura pode minimizar o edema.

Conclusão: Para prevenir complicações pós-operatórias associadas a terceiros molares impactados sem uso de terapias medicamentosas, dentre as técnicas estudadas, as mais eficientes classificadas por ordem decrescente são: cicatrização por segunda intenção; clorexidina como irrigante; aplicação de PRF; retalho envelope ou triangular; ponto contínuo festonado; e uso da CBTC em casos específicos. No entanto, novos estudos são necessários, especialmente para entender a influência da vitamina D3 e os efeitos da acupuntura.

Palavras-chave: “*postoperative complications*”, “*impacted teeth*”, “*molar, third*”, “*tooth extraction*”, “*treatment outcome*”.

ABSTRACT

Background: Impacted third molar surgery is a common procedure in dentistry. However, as any surgical procedure, it involves risks.

Objectives: The aim of this dissertation is to identify, systematise and categorise the non-pharmacological prevention methods of postoperative complications associated to the extraction of impacted third molars.

Material and methods: A search of the PubMed database was performed using a combination of keywords. The articles included were published between 2012 and 2022. The PRISMA 2020 flow diagram and the PICO methodology were used.

Results: Through the analysis of the articles it was found that: secondary closure reduces oedema, pain and trismus; the use of chlorhexidine minimises oedema, trismus, pain and alveolar osteitis; ozone and distilled water are comparable irrigating solutions; PRF can reduce oedema, trismus, pain, probing depth and improve healing; envelope and triangular flaps reduce oedema and trismus, and probing depth, respectively; horizontal mattress sutures decrease wound dehiscence; CBTC is more accurate in predicting nerve exposure compared to PAN; vitamin D3 can reduce oedema and pro-inflammatory factors; and acupuncture can minimise oedema.

Conclusion: To prevent postoperative complications associated with impacted third molars without using drug therapies, among the techniques reviewed, the most efficient sorted in descending order are: secondary closure; chlorhexidine as an irrigant; PRF application; envelope or triangular flaps; horizontal mattress sutures; and the use of CBTC in specific cases. Nonetheless, further studies are needed specially to understand the influence of vitamin D3 and the effects of acupuncture.

Keywords: “postoperative complications”, “impacted teeth”, “molar, third”, “tooth extraction”, “treatment outcome”.

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LIST OF ABREVIATIONS AND ACRONYMS

25(OH)D - 25-hydroxycholecalciferol (Calcifediol)

A-PRF - Advanced platelet-rich fibrin

BoP - Bleeding on probing

CAL - Clinical attachment loss

CBCT - Cone beam computed tomography

IAN - Inferior alveolar nerve

IL-1β - Interleukin-1-beta

IL-6 - Interleukin-6

IU - International Unit

L-PRF - Leukocyte platelet-rich fibrin

LN - Lingual nerve

mg/kg - Milligram per kilogram

ng/mL - Nanograms per millilitre

PAN - Panoramic radiography

PCR - C-reactive protein

pH - Potential hydrogen

PICO - Population, Intervention, Comparison, Outcome

PRF - Platelet-rich fibrin

PRP - Platelet-rich plasma

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT - Randomized control trials

rmp - Revolutions per minute

STAI - State trait anxiety inventory

TNF-α - Tumour necrosis factor-alpha

VAS - Visual analogue scale

1. INTRODUCTION

Impacted third molar surgery is one of the most frequent procedures in dentistry.[1–9] As any surgical procedure, it involves risks, even if it is done in the most minimal invasive way.[10] Some are associated with the simple fact that it is a surgical procedure, and that is enough to raise awareness about how to prevent its complications. Examples of these can be infections,[1,4,7,9] bleeding,[4,11,12] pain[1,2,4–9,11,13–15] and oedema.[3–5,9,13,16,17] Other risks are related to the anatomy of the posterior region of the maxilla and mandible. The fact that the last molars of both arches have a tendency to become impacted (*dens retens*)[18] in atypical positions that may be hard to extract,[18,19] is one of the reasons why these surgeries require such advanced surgical techniques, in order to be less traumatic to the surrounding tissues (bone, gingiva and neurovascular bundles), and to attain effectiveness and efficiency without compromising the patient's health or wellbeing.[7,20] Other than this, because the anatomy differs according to each dental arch, there are complications that only apply to maxillary surgeries, and others that are specific of mandibular surgeries.[21] In the maxilla, the complications can arise due to the presence of the maxillary tuberosity, that can fracture during the extraction of a third molar.[17,22,23] Also in this area, due to proximity to the pterygoid venous plexus and its tributary vessels (deep facial vein and posterior superior alveolar vein), there is the possibility, even though it is rare, of peri-orbital and subconjunctival ecchymosis.[24] Even though maxillary third molar extractions can lead to these complications, in the mandible the procedure can be more difficult due to the increased density of the bone, when compared to the maxilla, that has a more porous bone marrow, especially in the area of the tuberosity.[25] Nonetheless, the mandible is not anti-fracture, which means that all the precautions should be taken to prevent this complication, which can happen in different areas, such as the condyle or the angle of mandible, etc.[26] Other complications of the mandibular third molar surgery are damage to the inferior alveolar nerve (IAN) or lingual nerve (LN),[27–29] and this can cause an alteration of the patient's sensitivity (dysesthesia, paraesthesia or complete anaesthesia) in some areas of the face, specifically the ones enervated by the affected nerve.[6,29] The complications can be divided into two groups: the intraoperative and the postoperative complications.[13] Some intraoperative complications can be: bleeding,[4,11,12] root fracture,[13] soft tissue injury,[13,30] damage to the adjacent tooth,[13] oroantral

communication in the maxilla,[31,32] fracture of the tuberosity also in the maxilla,[17,22] and fracture of the mandible.[17,26] While some postoperative complications are: neurological damage to the IAN or LN in the mandible,[9,17,27,28] alveolar osteitis,[7,9,17,33] infections,[1,4,7,9] oedema,[1,3–5,9,13,16,17] pain,[1,2,4,5,7–9,11,13–15,17] trismus,[1,5,7–9,13,17,34] ecchymoses,[24] bleeding[4,11,12,22] and delay of wound healing.[4,7,35]

This review seeks to address specifically the different ways to prevent postoperative complications and recognize whether procedures can be ranked in a convenient order, that may assist the operator to choose the more effective prevention methods. This is attained through analysis of the findings of the studies researched, recognition of the methods that can help to control or prevent the complications, and comparison of information between articles in order to understand, if possible, the relative effectiveness of each prevention method, for the patient and operator's benefit. However, this review does not include, as the main comparison, any kind of drug therapy that may be used to prevent postoperative complications, other than irrigating solutions[2,15] normally used after an extraction. Yet, the majority of the articles use pharmacological therapies as part of the protocol,[1,3–5,7–9,13,15] nonetheless, they do not represent variables in those studies.

2. OBJECTIVES

The aim of this dissertation is to identify, systematise and categorise, through revision of the literature, the non-pharmacological prevention methods of postoperative complications associated to the extraction of impacted third molars. In order to attain this, it is important to understand the relation between each prevention method and the specific complications that it can prevent. Furthermore, prevention methods should be ordered with the purpose of constituting a useful tool for the operator in his clinical practice.

3. MATERIAL AND METHODS

3.1. Methodology

To conduct this integrative systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram was used, as well as the PICO (Population, Intervention, Comparison, Outcome) methodology. This latter was important in answering the following question:

- How is it possible to prevent postoperative complications associated with impacted third molars, without the use of drug therapies?

The PICO question is associated to the following criteria:

- Population: Individuals subjected to the extraction of impacted third molars.
- Intervention: To analyse postoperative complications associated with impacted third molars using specific non-pharmacological procedures.
- Comparison: To analyse postoperative complications associated with impacted third molars using a non-pharmacological control/placebo procedure.
- Outcome: To identify and systematise non-pharmacological prevention methods of postoperative complications.

3.2. Research strategy

A search of the PubMed electronic database (National Library of Medicine, Bethesda, MD) was performed using a combination of the following keywords: “postoperative complications”, “impacted teeth”, “molar, third”, “tooth extraction”, “treatment outcome”. With the following search string: ((((postoperative complications[MeSH Terms]) AND (impacted teeth[MeSH Terms])) AND (molar, third[MeSH Terms])) AND (tooth extraction[MeSH Terms])) AND (treatment outcome[MeSH Terms]).

3.3. Inclusion criteria

The inclusion criteria comprise articles published in the last 10 years (between 2012 and 2022), caried out in humans, in English, with specific study designs (Randomized control

trials and Clinical trials), which present relevant information associated with the non-pharmacological prevention of postoperative complications in the extraction of impacted third molars.

3.4. Exclusion criteria

The exclusion criteria applied include: publication date prior to 2012, articles in other languages, articles that do not have a title or abstract of interest (articles studying the effects of drug therapies and studying surgery techniques using different instruments), articles that do not focus on the appropriate population, and articles that do not adequately address the intervention/comparison presented in the PICO methodology. After this initial screening, other articles were excluded by full text reading.

3.5. Article selection

Table 1. Articles obtained and selected through the research.

Search string	Number of articles obtained	Number of articles selected
((((postoperative complications[MeSH Terms]) AND (impacted teeth[MeSH Terms])) AND (molar, third[MeSH Terms])) AND (tooth extraction[MeSH Terms])) AND (treatment outcome[MeSH Terms])	58	12

Of all the 58 articles identified through the research, 44 were excluded because they did not meet the eligibility requirements. The remaining studies were analysed, and 2 more articles were excluded in the second screening phase, through full text reading. In addition to these articles, 126 studies / books were included posteriorly from the PubMed database and citation searching to broaden the theoretical basis, which are also included in the references.

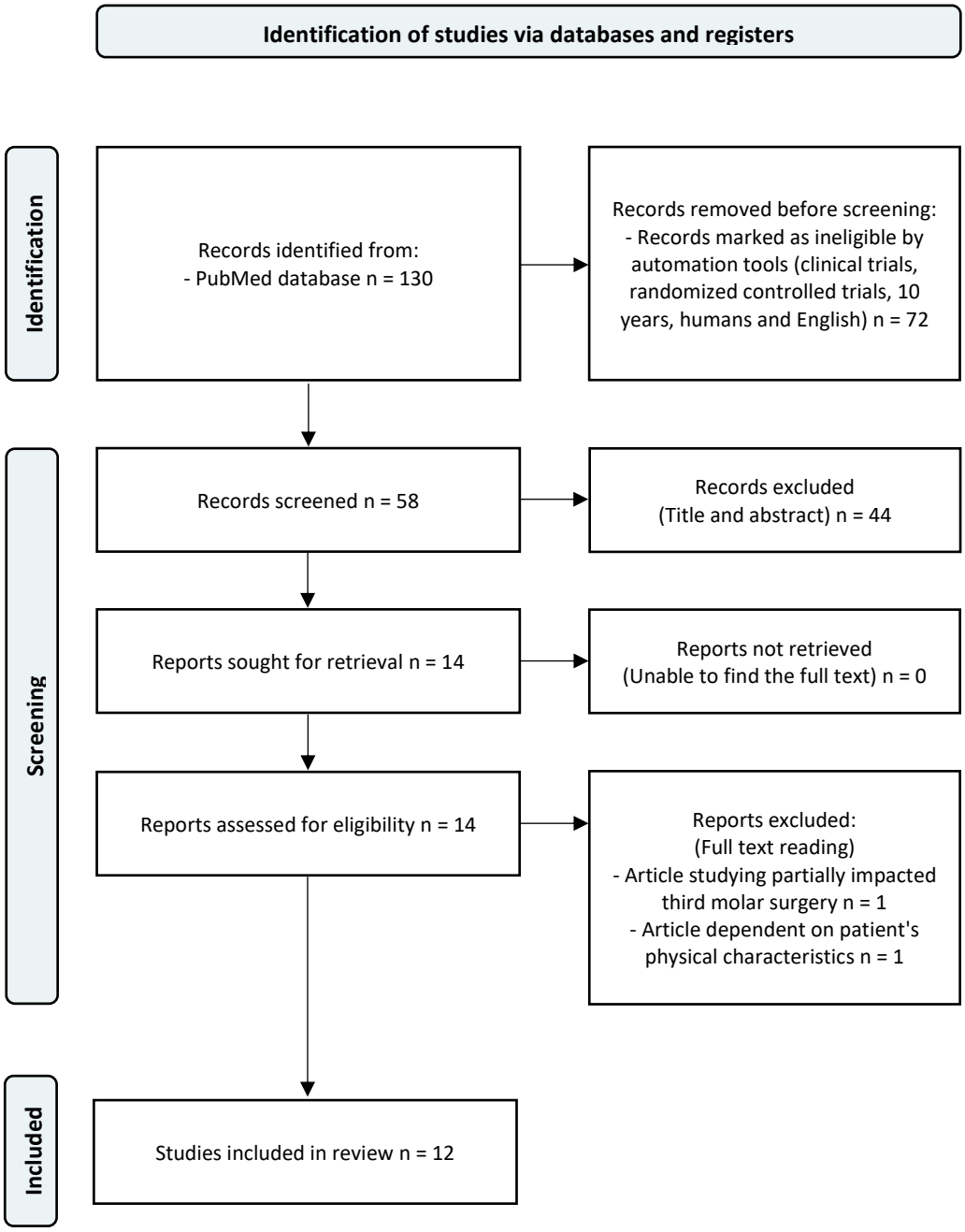

Figure 1. PRISMA 2020 flow diagram.

4. RESULTS

Table 2. Table of results based on the selected studies.

(Title, Author, Type of study, Year)	Population	Intervention	Comparison	Protocol	Findings	Outcomes
"Inferior Alveolar Nerve Sensory Disturbance After Impacted Mandibular Third Molar Evaluation Using Cone Beam Computed Tomography and Panoramic Radiography: A Pilot Study"[6] M. E. Guerrero, O. Nackaerts, J. Beinsberger, K. Horner, J. Schoenaers, R. Jacobs RCT 2012	79 patients with bilateral mandibular 3rd molars in close relation to the IAN showing a moderate risk of damaging the nerve - 86 surgical extractions	To measure sensory disturbances of the inferior alveolar nerve (IAN) after an extraction and the efficacy of the observer's prediction of IAN exposure using cone beam computed tomography (CBCT).	To measure sensory disturbances of the inferior alveolar nerve (IAN) after an extraction and the efficacy of the observer's prediction of IAN exposure using Panoramic radiography (PAN).	- PAN (risk categorization for all patients) - CBCT (only part of the patients) - 1 mm slice thickness - Assessment of the neurovascular function of the chin and lip - Evidence of close relation with the IAN (darkening of the root, loss of cortical margins or deviation of the canal) - Local anaesthesia - Mucoperiosteal flap - Ostectomy + tooth sectioning (coronectomy) + irrigation + extraction - Record of the exposure of the IAN	Neurosensory disturbances of the lip and chin (light-touch sensation method): baseline and 7th day - $p > 0.05$. Efficacy of prediction of IAN exposure: $p < 0.05$. No significant differences ($p > 0.05$): - Neurosensory disturbances of the lip and chin. With significant differences ($p < 0.05$): - Making a correct diagnosis of neurovascular bundle exposure (more accurate with CBCT - 56% compared to PAN - 35%).	CBCT is not superior to PAN in predicting sensory disturbances, only in predicting IAN exposure during the extraction.

"Does Vitamin D3 Have an Impact on Clinical and Biochemical Parameters Related to Third Molar Surgery"[14] G. Oteri, M. Cicciù, M. Peditto, A. Catalano, S. Loddo, M. Pisano, A. Lasco RCT 2016	25 vitamin D-deficient patients (blood levels ≤30 ng/mL) with bilateral mandibular 3rd molars class II level B and class II level C (Pell and Gregory) - 50 surgical extractions	Administration of 300000 IU of cholecalciferol 4 days before surgery.	Administration of placebo 4 days before surgery.	- Assessment of vitamin D3 blood levels - Administration of placebo or Cholecalciferol (4 days before) - Local anaesthetic - Full-thickness 4-cornered mucoperiosteal flap - Ostectomy when needed (irrigation: sterile saline) + tooth sectioning + extraction - Curettage + irrigation with normal saline - Simple interrupted sutures (5/0 Nylon), removed after 7 days	Oedema (face measurements): 4 days before, baseline and 3rd day - $p > 0.05$; 7th day - $p < 0.05$. Trismus (mouth opening): 4 days before, baseline, 3rd and 7th days - $p > 0.05$. Pain (visual analogue scale - VAS): 4 days before, baseline, 3rd and 7th days - no significant differences. Vitamin D3: placebo - $p > 0.01$; cholecalciferol - $p < 0.01$. C-reactive protein (PCR): 4 days before, baseline, 3rd and 7th days - $p > 0.05$. Tumour necrosis factor-alpha (TNF-α), Interleukin-1-beta (IL-1β), Interleukin-6 (IL-6): 4 days before and baseline - $p > 0.01$; 3rd and 7th days - $p < 0.01$. No significant differences: - Oedema (before 7th day - $p > 0.05$), trismus ($p > 0.05$), pain, vitamin D3 (when using placebo - $p > 0.01$), PCR ($p > 0.05$), TNF-α (before 3rd day - $p > 0.01$), IL-1β (before 3rd day - $p > 0.01$) and IL-6 (before 3rd day - $p > 0.01$)	Higher vitamin D serum levels showed an impact on the outcome of these surgeries, leading to a reduced inflammatory response and a more favourable clinical course, especially regarding oedema.

					With significant differences: - Oedema (greater when using placebo 7th day - $p < 0.05$), vitamin D3 (greater when using cholecalciferol - $p < 0.01$), TNF-α (greater when using placebo 3rd and 7th days - $p < 0.01$), IL-1β (greater when using placebo 3rd and 7th days - $p < 0.01$) and IL-6 (greater when using placebo 3rd and 7th days - $p < 0.01$).	
"Flap design and mandibular third molar surgery: a split mouth randomized clinical study"[7] Z. H. Baqain, A. Al-Shafii, A. A. Hamdan, F. A. Sawair RCT 2012	19 patients with bilateral mandibular 3rd molars - 38 surgical extractions	Envelope flap design was performed before extraction.	Triangular flap design was performed before extraction.	- PAN (position of 3rd molar - 0.03 mg/kg midazolam (more if needed); 8 mg dexamethasone; 1 g amoxicillin + clavulanic acid - Lidocaine + adrenaline - Envelope or triangular flap design - Ostectomy (irrigation: normal saline) + tooth sectioning (if needed) + extraction - Curettage + irrigation with normal saline - Sutures (4/0 silk thread)	Oedema (face measurements): 2nd and 7th days - $p < 0.05$; 14th day - $p > 0.05$. Trismus (mouth opening): 2nd day - $p > 0.05$; 7th and 14th days - $p < 0.05$. Pain (VAS): 2nd, 7th and 14th days - $p > 0.05$). Infection / alveolar osteitis: no record. Plaque index (PI) and bleeding on probing (BoP): preoperative, 7th and 14th days - $p > 0.05$. Periodontal probing depth (distal aspect of the mandibular 2nd molar): 7th, 14th days and 17 week - $p < 0.01$. Wound dehiscence - $p > 0.05$.	Flap design in mandibular 3rd molar surgery effects the postoperative recovery.

				- Non-steroidal analgesic 5 days + mouth wash	No significant differences ($p > 0.05$): - Oedema (14th day), trismus (2nd day), pain, PI, BoP and wound dehiscence. With significant differences: - Oedema (greater with triangular flaps before 14th day - $p < 0.05$), trismus (greater with triangular flaps after 7th day - $p < 0.05$) and probing depth (greater with envelop flaps - $p < 0.01$).	
"Comparison of a new flap design with the routinely used triangular flap design in third molar surgery"[9] Ü. Yolcu, A. H. Acar RCT 2015	22 patients with mesially angulated mandibular 3rd molars (Winter) - 44 surgical extractions	Lingually based triangular flap design was performed before extraction.	Triangular flap design was performed before extraction.	- 2 sessions (4-week interval) - extraction of one tooth per session with different flaps - Povidone iodine mouth rinse - Articaine + epinephrine - Triangular flap or lingually based triangular design - Ostectomy (irrigation: normal saline) + tooth sectioning (if needed) + extraction - 6 simple interrupted sutures (buccally based flap) or 7 simple interrupted sutures	Oedema (face measurements): 2nd, 7th, 14th and 21st days - $p > 0.05$. Trismus (mouth opening): preoperative, 2nd, 7th, 14th and 21st days - $p > 0.05$. Pain (VAS): 12h - $p < 0.05$; 6h, 1st, 2nd, 3rd, 4th, 5th, 6th and 7th days - $p > 0.05$. Wound dehiscence: 7th, 14th and 21st days - $p > 0.05$. No significant differences ($p > 0.05$): - Oedema, trismus and wound dehiscence (greater with triangular flaps).	Both flap designs are comparable, however the triangular flap design shows a greater reduction in pain scores and the lingually based triangular flap design is preferable in wound healing.

				(lingually based flap) (4/0 silk thread), removed after 7 days - 500 mg paracetamol 3 days; chlorhexidine gluconate + benzydamine hydrochloride 5 days	With significant differences ($p < 0.05$): - Pain (greater with lingually based triangular flaps 12h after surgery).	
"Influence of ozonized water on pain, oedema, and trismus during impacted third molar surgery: a randomized, triple blind clinical trial"[2] J. C. R. G., D. W. Douglas-de-Oliveira, L. D. A. E. Silva, S. G. M. Falci and C. R. R. D. Santos RCT 2020	20 patients with bilateral mandibular 3rd molars class II level B (Pell and Gregory) - 40 surgical extractions	Irrigation with ozonized double distilled water.	Irrigation with double distilled water. (Clear, hypotonic, sterile and pyrogenic solution.)	- Iodized polyvinylpyrrolidone-iodine alcohol solution at 10% (extra oral antisepsis) - Lidocaine + epinephrine - Flap design by Avellanal, 1946 - Ostectomy (irrigation: ozonized or double distilled water) + loosening of the tooth (Seldin elevator) + extraction - Curettage + bone regularization + irrigation - Simple interrupted sutures (4/0 silk thread), removed after 7 days	Oedema (face measurements): baseline, 1st, 2nd, 3rd and 7th days - $p > 0.05$. Trismus (mouth opening): 1st, 2nd, 3rd and 7th days - $p > 0.05$. Pain (VAS): 1st, 2nd and 3rd days - $p > 0.05$ (greater pain with ozonized 1st day). No significant differences ($p > 0.05$): - Oedema (greater at baseline; began to resume normal 7th day), trismus (significant reduction of mouth opening compared to baseline) and pain (greater with ozonized water 1st day; greater with double distilled water 3rd day).	Ozonized water is a comparable irrigation method to double distilled water.

"The Efficiency of Three Irrigating Solutions after Surgical Removal of Impacted Mandibular Third Molars: A Cross-sectional Study"[15] V. A. Jadhao, A. Rao, P. Hande, M. Mahajani, P.P. Raktade, R. Gedam, V. Acharya, P. D. Tekale RCT 2015	48 patients with bilateral mesioangular mandibular 3rd molars (Winter) / level B (Pell and Gregory) - 48 surgical extractions	Irrigation with chlorhexidine after the extraction. - or - Irrigation with povidone iodine after the extraction.	Irrigation with normal saline after the extraction.	- Lidocaine + adrenaline - L-shaped flap - Ostectomy (irrigation: 0,02% chlorhexidine, 0,5% povidone iodine or normal saline) + extraction - Sutures (3/0 plain gut absorbable thread) - 500 mg amoxicillin + 125 mg clavulanic acid 2x/day; 1000 mg paracetamol every 4-6h (if needed); 150 mg ranitidine 2x/day maximum 7 days	Oedema (face measurements): 1st day - $p < 0.01$; 7th day - $p > 0.01$. Trismus (mouth opening): 7th day - $p < 0.01$. Pain (VAS): 1st and 7th days - $p < 0.01$. Alveolar osteitis: 7th day - $p < 0.01$. Infection: 7th day - $p > 0.01$. Food impaction: 7th day - $p > 0.01$. No significant differences ($p > 0.01$): - Oedema (7th day), infection and food impaction. With significant differences ($p < 0.01$): - Oedema (greater when using normal saline and povidone iodine 1st day), trismus (greater when using normal saline and povidone iodine), pain (greater when using normal saline and povidone iodine) and alveolar osteitis (not reported when using chlorhexidine).	Chlorhexidine reduces oedema (especially during the 1st postoperative day), trismus, pain and alveolar osteitis when applied as an irrigant in the removal of impacted third molars.

"Comparison of the effect of advanced platelet-rich fibrin and leukocyte- and platelet-rich fibrin on outcomes after removal of impacted mandibular third molar: A randomized split-mouth study"[3] MG Caymaz and LO Uyanık RCT 2022	27 patients with bilateral vertically angulated mandibular 3rd molars (Winter) / class I level C (Pell and Gregory) - 54 surgical extractions	Application of advanced platelet-rich fibrin (A-PRF) at the extraction site.	Application of leukocyte platelet-rich fibrin (L-PRF) at the extraction site.	- 2 sessions (21 days interval) - extraction of one tooth per session with different types of PRF applications (A-PRF preparation: 14 min - 1500 rpm / L-PRF preparation: 14 min - 3000 rpm) - PAN - Articaine + epinephrine - Triangular flap design - Osteotomy (irrigation) + loosening of the tooth (root elevator) + extraction - Irrigation (normal saline) - A-PRF application or L-PRF application - 4 Simple interrupted sutures (3/0 thread), removed after 7 days - 875 mg amoxicillin + 125 mg clavulanic acid 2x/day, 5 days; 7,5% povidone iodine 3x/day, 7 days; 500 mg acetaminophen every 4-6h (if needed)	Oedema (face measurements): 1st, 2nd, 3rd, 7th days - $p > 0.05$. Trismus (mouth opening): 1st, 2nd, 3rd, 7th days - $p > 0.05$. Pain (VAS): 1st day - $p < 0.05$; 2nd and 3rd days - $p < 0.01$; 7th day - $p > 0.05$. Number of analgesics taken: 1st and 7th days - $p > 0.05$; 2nd day - $p < 0.01$; 3rd day - $p < 0.05$. No significant differences ($p > 0.05$): - Oedema, trismus, pain (7th day) and number of analgesics taken (1st and 7th days). With significant differences: - Pain (greater when using L-PRF 1st day - $p < 0.05$, 2nd and 3rd days - $p < 0.01$) and number of analgesics taken (greater when using L-PRF 2nd day - $p < 0.01$, 3rd day - $p < 0.05$).	The use of A-PRF compared to L-PRF, significantly reduces postoperative pain and the patient's need to take analgesics.

"Evaluation of treatment outcome after impacted mandibular third molar surgery with the use of autologous platelet rich fibrin: a randomized controlled clinical study"[13] N. Kumar, K. Prasad, R. Ramanujam, K. Ranganath, J. Dexith and A. Chauhan RCT 2015	31 patients with mesioangular or horizontally impacted mandibular 3rd molars (Winter) - 31 surgical extractions	PRF was placed in the socket followed by primary closure.	Only primary closure was performed at the extraction site.	- (PRF preparation: 10 min - 3000 rpm) - Intraoral periapical radiograph of the impacted molars + PAN - Oral prophylaxis + gingival index + plaque index + periodontal probing depth - Lidocaine + adrenalin - Modified Ward's incision - Ostectomy + tooth sectioning (if needed) + loosening of the tooth (elevator) + extraction - Irrigation + curettage + bone regularization - PRF application or no intervention - Sutures (3/0 silk thread), removed after 7 days - 500 mg amoxicillin 3x/day, 3 days; 400 mg metronidazole 3x/day, 3 days; aceclofenac + paracetamol 2x/day, 3 days; chlorhexidine 3x/day, 3 days	Oedema (VAS): 1st day - $p < 0.05$. Trismus (mouth opening): 1st day - $p < 0.05$. Pain (VAS): 1st day - $p < 0.05$. Periodontal probing depth: preoperative, 1st and 3rd months - $p < 0.05$ (without PRF) and $p < 0.01$ (with PRF) - Intragroup analysis. Bone formation (radiographic exams): 3rd month - $p > 0.05$. No significant differences ($p > 0.05$): - Bone formation. With significant differences: - Oedema (greater without using PRF - $p < 0.05$), trismus (greater without using PRF - $p < 0.05$), pain (greater without using PRF - $p < 0.05$) and periodontal probing depth (reduction without PRF - $p < 0.05$, reduction with PRF - $p < 0.01$).	Application of PRF lessens the severity of postoperative complications and increases bone formation.

"Influence of leukocyte- and platelet-rich fibrin (L-PRF) on the outcomes of impacted mandibular third molar removal surgery: A split-mouth randomized clinical trial"[4] P. Daugela, V. Grimuta, D. Sakavicius, J. Jonaitis and G. Juodzbalys RCT 2018	30 patients with bilateral mandibular 3rd molars - 60 surgical extractions	Application of leukocyte platelet-rich fibrin (L-PRF) at the extraction site.	Allow blood clot formation after extraction, without L-PRF application.	- (PRF preparation: 12 min - 2800 rpm) - PAN and/or CBCT - 600 mg clindamycin 1h before the procedure - Local anaesthetic - Mucoperiosteal flap - Ostectomy + tooth sectioning (coronectomy and root separation) + loosening of the tooth + extraction - Curettage - PRF application or no intervention - Simple interrupted sutures (5/0 polyglactin absorbable thread), removed after 7 days - 600 mg clindamycin 6h after the procedure; 8 mg lornoxicam (if needed); 0,12% chlorhexidine 3x/day, 2 weeks	Oedema (face measurements): preoperative and 7th day - $p > 0.05$; 1st and 3rd days - $p < 0.05$. Pain (VAS): 1st, 2nd, 3rd, 4th, 5th, 6th, 7th days - $p < 0.01$. Wound healing (bleeding, suppuration, tissue colour and consistency): 1st, 3rd and 7th days - $p < 0.01$; 14th day - $p < 0.05$. Alveolar osteitis: $p < 0.01$. No significant differences ($p > 0.05$): - Oedema (preoperative and 7th day). With significant differences: - Oedema (greater without using L-PRF 1st and 3rd days - $p < 0.05$), pain (greater without using L-PRF - $p < 0.01$), wound healing (greater when using L-PRF 1st, 3rd and 7th days - $p < 0.01$, 14th day - $p < 0.05$) and alveolar osteitis (not reported when using PRF - $p < 0.01$).	L-PRF improves wound healing, reduces oedema, pain, and incidence of alveolar osteitis.

"Comparative study of primary and secondary closure of the surgical wound after removal of impacted mandibular third molars"[5] P. K. Pachipulusu, S. Manjula RCT 2018	60 patients with bilateral mandibular 3rd molars - 60 surgical extractions	Primary closure at the extraction site.	Secondary closure at the extraction site.	- Intraoral periapical radiograph of the impacted molars + PAN - Local anaesthetic - Mucoperiosteal flap - Ostectomy + extraction - Removal of 5 - 6 mm of mucosa from the buccal flap (only secondary closure) - Various simple interrupted sutures or only 2 simple interrupted sutures at the wound edges (3/0 black silk or polyglactin thread), removed after 7 days - 500 mg amoxicillin + 125 mg clavulanic acid 5 days, aceclofenac + paracetamol 5 days	Oedema (face measurements): 1st, 3rd and 7th days - $p < 0.001$. Trismus (mouth opening): 1st, 3rd and 7th days - $p < 0.002$. Pain (VAS): 1st, 3rd and 7th days - $p < 0.001$. Periodontal probing depth (distal aspect of the mandibular 2nd molar): preoperative and postoperative - $p > 0.05$. Alveolar osteitis: 1 patient with secondary healing. No significant differences ($p > 0.05$): - Periodontal probing depth. With significant differences: - Oedema (higher with primary closure - $p < 0.001$), trismus (higher with primary closure - $p < 0.002$) and pain (higher with primary closure - $p < 0.001$).	Secondary closure is better than primary closure regarding oedema, trismus and pain. There is no difference on the probing depth regardless of the closure technique.

"Is Horizontal Mattress Suturing More Effective Than Simple Interrupted Suturing on Postoperative Complications and Primary Wound Healing After Impacted Mandibular Third Molar Surgery?"[1] A. H. Acar, H. O. Kazancioglu, N. F. Erdem and F. Asutay RCT 2017	30 patients with bilateral mandibular third molars class III level B (Pell and Gregory) - 60 surgical extractions	Flaps were sutured with the horizontal mattress suturing technique.	Flaps were sutured with the simple interrupted suturing technique.	- 2 sessions (4-week interval) - extraction of one tooth per session with different suturing techniques - 0,2% chlorhexidine mouth rinse - Articaine + epinephrine - Triangular flap design - Ostectomy (irrigation: normal saline) + tooth sectioning + extraction - 2 simple interrupted sutures - vertical releasing incision (3/0 synthetic silk thread) - 3 simple interrupted sutures or 2 horizontal mattress sutures (3/0 synthetic silk thread) - 300 mg etodolac 3x/day; 1000 mg amoxicillin 2x/day; 2% chlorhexidine gluconate 5 days	Oedema (face measurements): 2nd, 7th and 10th days - $p > 0.05$. Trismus (mouth opening): 2nd, 7th and 10th days - $p > 0.05$. Pain (VAS): 6, 12 hours and 1st, 2nd, 3rd, 4th, 5th, 6th and 7th days - $p > 0.05$. Wound dehiscence: 10th day - $p < 0.05$. No significant differences ($p > 0.05$): - Oedema, trismus and pain. With significant differences ($p = 0,017$): - Wound dehiscence (reduced with horizontal mattress suturing; greater with simple interrupted suturing).	Horizontal mattress suturing technique is more effective than the simple interrupted suturing technique on wound healing, although it does not decrease the levels of pain, trismus, and oedema.

"Acupuncture on anxiety and inflammatory events following surgery of mandibular third molars: a split-mouth, randomized, triple-blind clinical trial"[8] A. C. V. Armond, J. C. R. Glória, C. R. R. D. Santos, R. Galo, S. G. M. Falci RCT 2018	16 patients with bilateral mandibular 3rd molars class II level B (Pell and Gregory) - 32 surgical extractions	Use of acupuncture in controlling postoperative complications.	Use of placebo acupuncture in controlling postoperative complications.	- 8 mg dexamethasone 1h before surgery - 2 sessions (45 days interval) - extraction of one tooth per session with acupuncture or placebo - 0.2% chlorhexidine digluconate mouth rinse 1 min - Iodized polyvinylpyrrolidone-iodine alcohol solution at 10% (extra oral antisepsis) - Lidocaine + epinephrine - Mucoperiosteal flap - Ostectomy (irrigation: normal saline) + tooth sectioning + loosening of the tooth (Seldin elevator) + extraction - Curettage + bone regularization + irrigation - Simple interrupted sutures (4/0 silk thread), removed after 7 days	Oedema (face measurements): 1st day - $p > 0.05$; 2nd, 3rd and 7th days - $p < 0.05$. Trismus (mouth opening): 1st, 2nd, 3rd and 7th days - $p > 0.05$. Pain (VAS): 1st, 2nd and 3rd days - $p > 0.05$. Anxiety (Spielberger state trait anxiety inventory - STAI + VAS): $p > 0.05$. Number of analgesics taken: $p > 0.05$. No significant differences ($p > 0.05$): - Trismus, pain, anxiety and number of analgesics taken. With significant differences ($p < 0.05$): - Oedema (greater when using placebo acupuncture since the 2nd day - $p < 0.05$).	Acupuncture achieves better results in the control of oedema when compared to placebo acupuncture.

				- 0,12% chlorhexidine digluconate every 12h, 2nd to 7th day; 750 mg paracetamol 1x/day, every 6h (if needed) - Insertion of active needles (0,25 x 30 mm) or insertion of placebo needles (0,25 x 25 mm) in eleven different points based on Traditional Chinese Medicine (30 min before surgery, 1st, 2nd and 3rd days postoperatively)		

5. DISCUSSION

5.1. Tooth impaction

Maxillary and mandibular third molars can be partially or completely impacted, and combined they account for 98% of all impacted teeth in the oral cavity.[3,36,37] Regarding tooth impaction, it can be defined as the failure to completely erupt into a correct position during the amount of time normally required due to lack of space (Figure 2).[36,38] It is also important to note that there is a difference between impacted and unerupted teeth. When a tooth is referred as unerupted, means it has not erupted within the physiological time, however, it shows radiographic evidence of eruptive capacity without any obstruction on its eruptive path.[39] Since mandibular third molars have a higher percentage of impaction compared to maxillary third molars,[40,41] and are also the most frequently impacted teeth,[40,42] almost all the selected studies focuses on the lower jaw[1–4,6–9,13,15] The incidence of the presence of both mandibular third molars in the population is 90%, with 33% presenting at least one of them impacted.[9,36]

Figure 2: 28 and 38 impacted. *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

5.1.1. Factors of tooth impaction

There are different types of factors that can lead to tooth impaction, which can be divided into two groups: local and systemic, depending on the aetiology.[38,44–47] Some local factors are: root dilaceration, trauma,[44–46,48] lack of space in the dental arch, ankylosis of the

deciduous teeth, ectopic positioning of tooth buds, pathological lesions,[38,44–46,48–50] supernumerary teeth, cleft lip and palate, etc.[38,49,50] Systemic factors can be: incorrect nutrition, rickets, vitamin D deficiency, syndromes, specific infections,[44] endocrine diseases,[38,44,51] cleidocranial dysplasia, down syndrome, febrile diseases, etc.[38,51]

5.1.2. Classification of impacted third molars

Considering classification of impacted third molars, several methods have been identified and the most commonly used are Pell and Gregory, and Winter's classification.[38,43] Pell and Gregory describe tooth impaction based on two different variables related to the tooth's position, in regard to the second molar and the ramus of the mandible (Figure 3).[38,40,43,52] Winter just focuses on third molar angulation types in relation to the adjacent second molar (Figure 4).[38,43] The studies selected in this review use either one[1,2,8,9,13] or both[3,15] of these classifications, therefore, it is relevant to explain them in further detail.

In the case of Pell and Gregory's classification, an impacted third molar can be classified into three classes[40,43] and three levels.[38,43] The classes are described in accordance with the relation to the mandibular ramus.[40,43] Class I, when the tooth is positioned anterior to the anterior border of the ramus; class II, when half of the crown is positioned anterior to the anterior border of the ramus; and class III, if the whole crown is covered by the anterior border of the ramus.[40] In the case of maxillary third molars, classes are defined in relation to the second molar and maxillary tuberosity.[43] The levels can be A, B or C, depending on the position of the third molar in regard to the occlusal plane and cervical line of the adjacent second molar. Level A, when the tooth is at the same level or above the occlusal surface of the second molar; level B, if the tooth is between the occlusal surface and the cervical line of the second molar; and level C, when located below the cervical line of the second molar.[38,43,52] Regarding Winter's classification, the different types of angulation are: vertical (10º to -10º), mesioangular (11º to 79º), horizontal (80º to 100º), distoangular (-11º to -79º) and other types (101º to -80º), where buccolingual[38] and inverted impactions[43] are included.

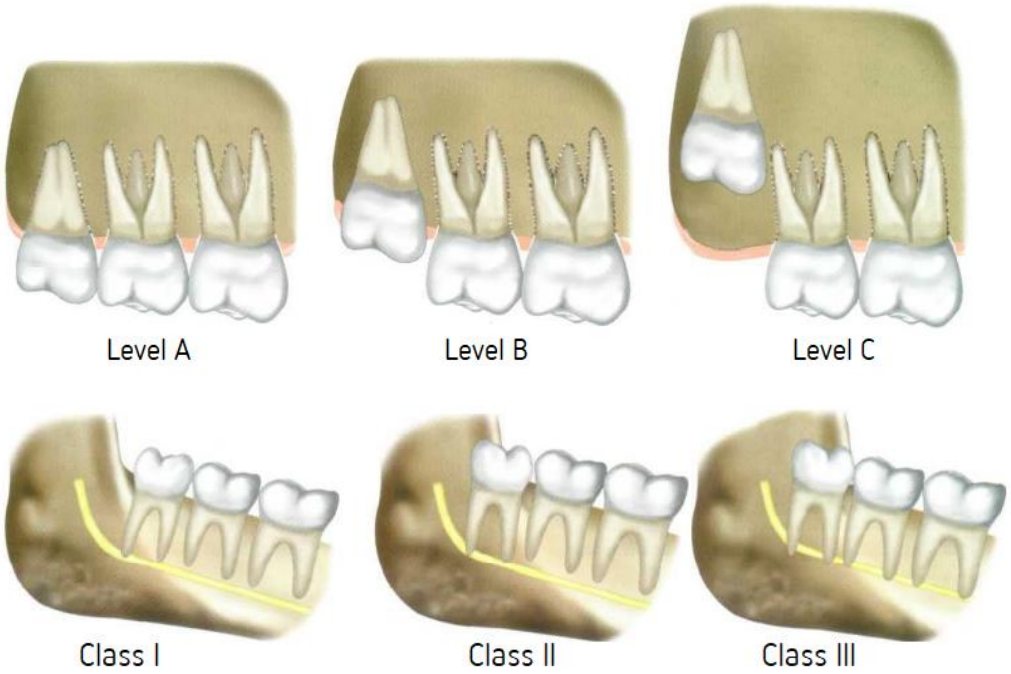

Figure 3: Pell and Gregory's classification. *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

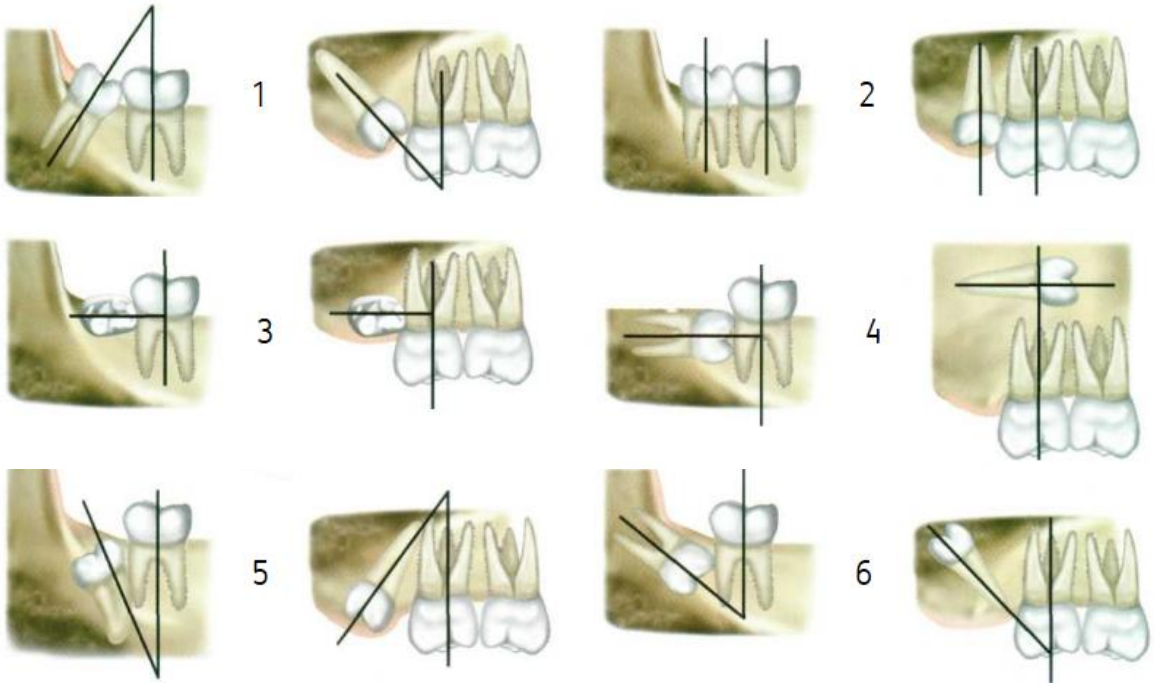

Figure 4: Winter's classification. 1 - Mesioangular, 2 - Vertical, 3 - Buccolingual, 4 - Horizontal, 5 - Distoangular, 6 - Inverted. *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

5.2. Anatomical structures

Concerning anatomical features, both maxillary and mandibular third molars are close to important structures that must be taken into account at the moment of extraction.[43]

5.2.1. Anatomical structures related to the maxillary third molar

The maxillary third molar, during its development, delineates a path from a more superior area within the maxillary tuberosity towards the alveolar ridge, between the second molar and the pterygomaxillary fissure. Besides, an upper third molar is also related to the maxillary sinus and the pterygomaxillary region.[43] This is the region where the pterygoid venous plexus is located (Figure 5). In some cases, if the plexus or one of its tributary veins, such as the deep facial vein or the posterior superior alveolar vessels are affected or injured in some way, this may cause a postoperative haemorrhage that can lead to peri-orbital, subconjunctival ecchymosis and ecchymosis in the buccal mucosa (Figure 6).[22,24] Specifically about the maxillary sinus, it is an important structure because it maintains a close relationship with the upper third molar during all its developmental stages, and in some situations the only physical separation between them is a very thin layer of bone. Referring to tooth angulation, their axis usually derivate outward, towards the vestibule, and more rarely obliquely, towards the second molar. Due to the high prevalence of maxillary hypoplasia and small-sized dental arches, only approximately 20% of them erupt in a normal position. Furthermore, the eruption pattern of these molars can also be influenced according to the resistance of the surrounding cortical bone. Since the outer cortical bone is denser than the inner one, these teeth can also erupt in a more lingual position.[43]

5.2.2. Anatomical structures related to the mandibular third molar

Considering mandibular third molars, they normally become impacted due to insufficient space in the mandible. With the evolutionary process, the retromolar space has been progressively decreasing, however this is not the case concerning the size of the teeth. The anatomical structures that further aggravate this lack of space are: the adjacent mandibular second molar, the neurovascular bundle containing the IAN, and the oral mucosa; in an anterior, inferior and superior position, respectively. The mucosa, unable to retract due to

the third molar's presence, can lead to periodontal defects where microorganisms may multiply and cause infection. Lower third molars are also closely related with the masseterine, genian and vestibular region, the temporal space, the pterygomaxillary region, the anterior faucial pillar, the peritonsillar space, as well as the soft palate. In regard to the IAN, its course begins on the inner side of the mandibular ramus, passing through the mandibular foramen, near the spix's spine, and continues its path towards the premolar area (Figure 7). It is also important to note that during this course, the neurovascular bundle is lined with a layer of cortical bone.[43]

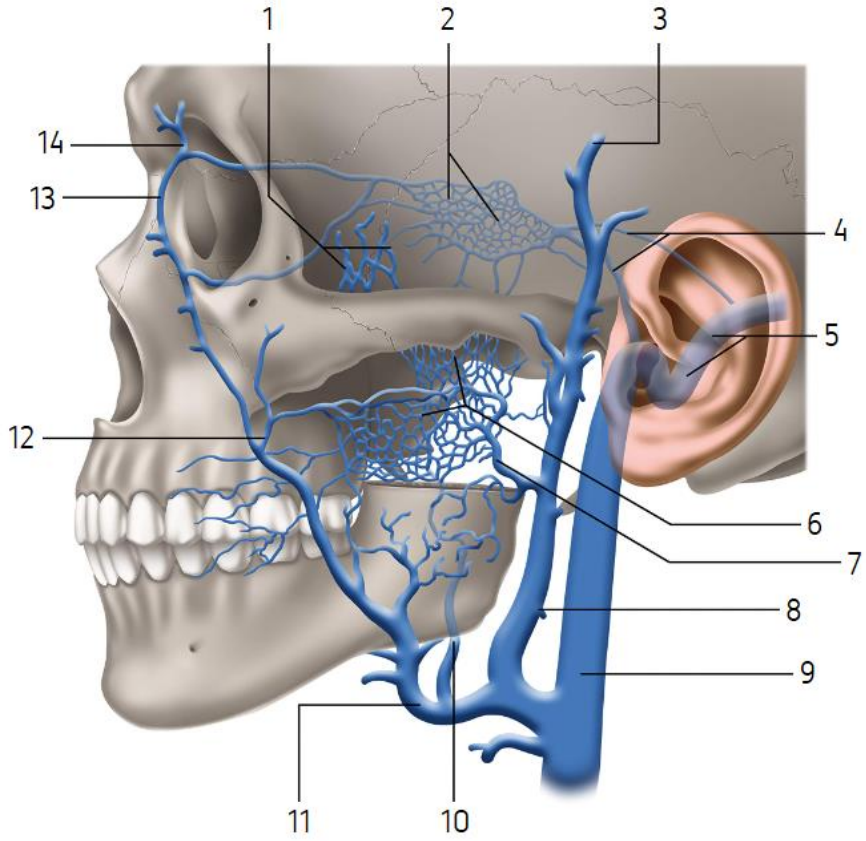

Figure 5: Facial veins. 1 - Deep temporal vein, 2 - Cavernous sinus, 3 - Superficial temporal vein, 4 - Superior and inferior petrosal sinuses, 5 - Sigmoid sinus, 6 - Pterygoid plexus, 7 - Maxillary vein, 8 - Retromandibular vein, 9 - Internal jugular, 10 - External palatine vein, 11 - Facial vein, 12 - Deep facial vein, 13 - Angular vein, 14 - Superior ophthalmic vein. *IN* Holtzclaw D. Pterygoid Implants: The Art and Science. Holtzclaw D, editor. DIA Management Services INC; 2020.[53]

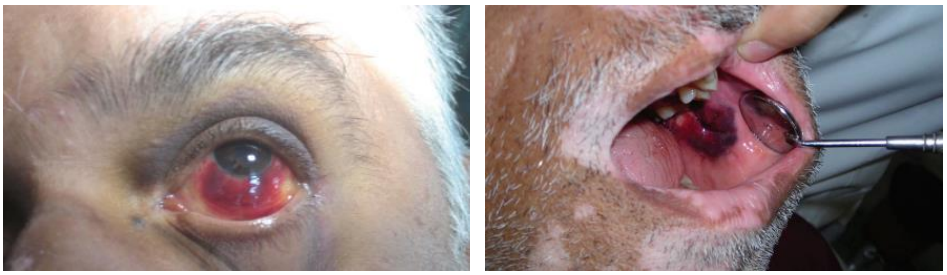

Figure 6: Postoperative haemorrhage. Peri-orbital and subconjunctival ecchymosis, on the right; ecchymosis in the buccal mucosa, on the left. *IN* Thirumurugan K. Maxillary tuberosity fracture and subconjunctival hemorrhage following extraction of maxillary third mola. J Nat Sci Biol Med. 2013;4(1):242–5.[22]

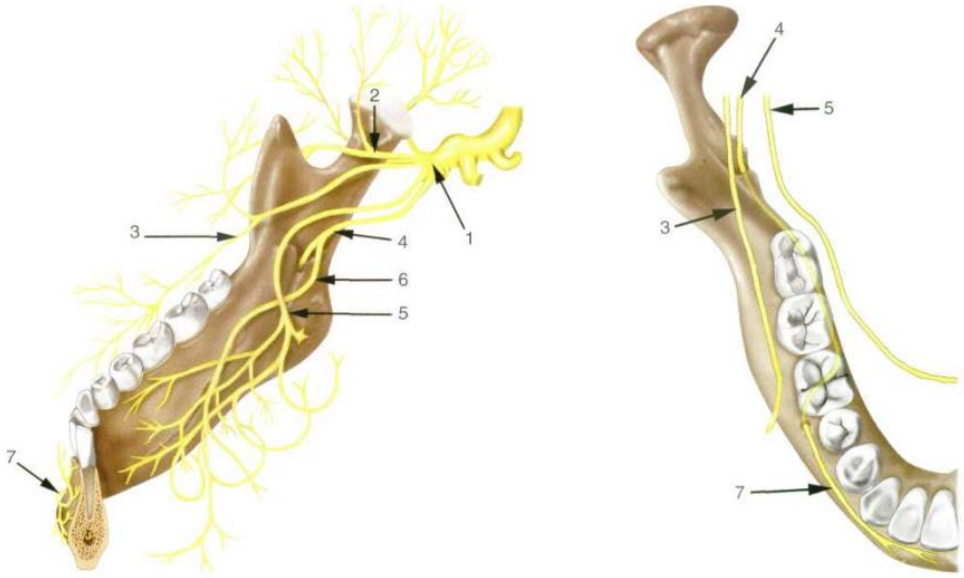

Figure 7: Mandibular nerves. 1 - Mandibular nerve (V3), 2 - Anterior deep temporal nerve, 3 - Buccal nerve, 4 - Inferior alveolar nerve, 5 - Lingual nerve, 6 - Mylohyoid nerve, 7 - Mental nerve. *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

5.3. Third molar extraction and associated postoperative complications

The removal of third molars is one of the most performed procedures in dentistry.[1,3–9,54–58] Some of the motives for their extraction are: damage of second molars, pain, proximity to mandibular fracture line or orthognathic surgery site, infection prophylaxis for cardiac surgery and endocarditis, prosthodontic reasons,[4,59] orthodontic reasons, presence or risk of caries, infections, presence of cysts or tumours,[4,8,59] and periodontal problems[8]. Even though it is very common, this type of surgery can lead to various complications.[1,2–9,13–15]

In regard to postoperative complications, which are the focus of this integrative review, previous studies find that their incidence following third molar surgery is higher in patients over 25 years old.[13,60,61] Some of the complications can be: neurological damage to the IAN or LN in the mandible,[9,17,27,28] alveolar osteitis,[7,9,17,33] infections,[1,4,7,9] oedema,[1,3–5,9,13,16,17] pain,[1,2,4,5,7–9,11,14,15,17] trismus,[1,5,7–9,11,13,17,34] ecchymoses,[22,24] bleeding,[4,11,12,22] delay of wound healing[4,7,35] and increased periodontal probing depth on the distal aspect of the second molar.[5,7,13] It is important to note that the latter can be misinterpreted as a complication, if the operator does not take into account some factors. In case of close relation between the second and third molar, the probing depth may not be registered correctly due to the restriction caused by the third molar. If this occurs preoperatively, the probing depth after third molar extraction may be greater, leading the operator to consider a further increase in depth compared to the actual value.[13]

5.4. Surgical procedure

The main objective in this type of surgical procedure is to remove the teeth that are indicated for extraction, while being as atraumatic as possible to the surrounding tissues and preventing postoperative complications as a means to reduce patient discomfort.[4] Before starting the procedure, the operator needs to evaluate the pros and cons of extracting an impacted tooth.[7,43] In some situations, the extraction may not the best solution, for example when there is a clear, undeniable proximity to the IAN.[62] When the surgical procedure is indicated, the technique is usually characterized by administration of local anaesthetic, incision and flap design, ostectomy[1–9,13–15] (Figure 8), irrigation[1–3,6–9,13,14] (Figure 8), tooth sectioning[1,2,6–9,13,14] (Figure 9), extraction of the tooth,[1–9,13–15] curettage[2,4,7,8,13,14] and suture technique.[1–5,7–9,13,14] Not all authors of the articles studied in this integrative review use the same method. Some of them do not perform sutures[6,8] or tooth sectioning,[4,5,15] for example; while others may add pharmacological therapies[1,3–5,7–9,13,15] to the basic protocol. However, comparisons with the intent to understand the effectiveness of certain drug therapies are not the focus of any of the studies.

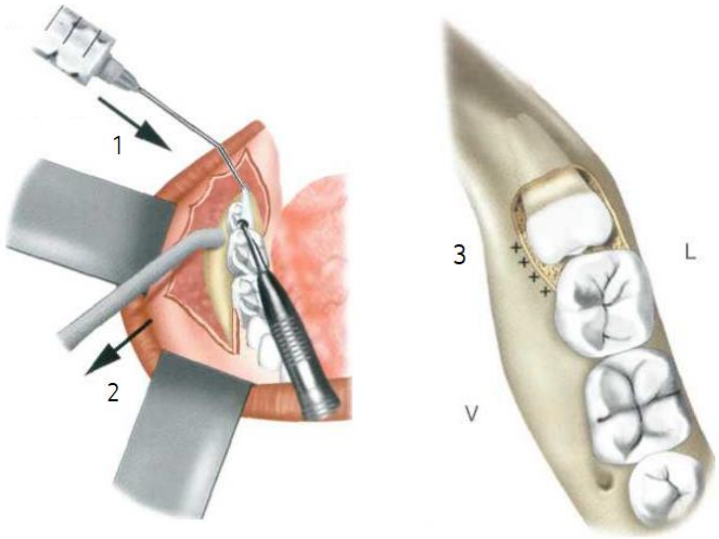

Figure 8: Surgical procedure. 1 - Irrigation, 2 - Aspiration, 3 - Ostectomy. *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

Figure 9: Tooth sectioning. *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

5.5. The use of panoramic radiography and cone beam computed tomography

The removal of a mandibular third molar is a procedure that involves risk of injury to the IAN and LN,[6,27,28] which is the most serious complication of this surgery because it can cause an alteration in sensory perception.[6] The incidence of this alteration varies from 0.4% to 13.4%,[6,63,64] and it manifests itself as dysesthesia (abnormal sensation),[6] paraesthesia (sensation of tingling, numbness or burning)[65,66] or anaesthesia (loss of sensation).[65] The incidence of affecting permanently the IAN and LN is 0,4%[6,63] to 13,4%[6,64] and 0%[6,67] to 11%,[6] respectively. In order to avoid sensory alterations, it is important to determine the distance between that apex of the tooth and the neurovascular

bundle, and identify radiographic risk factors that may cause complications.[6,68,69] The radiographic exams used to prevent nerve injuries are the PAN and CBCT.[6] Nonetheless, according to Tantanapornkul *et al*[70], the latter is more effective in predicting IAN exposure and consecutively reduce the risk of nerve injury,[6,70] even though nerve exposure does not always mean nerve damage, it depends on the operator's training, skills and experience.[6,71–73] In contrast, the findings of Ghaeminia *et al*[74] are not similar.[6] The study conducted by Guerrero *et al*[6] compares these two exams with the intent to understand if there is a significant difference between the incidence of nerve injuries, and how well the observers predict IAN exposure based on the information gathered from the exams. Finally the results of Guerrero *et al*[6] match the findings of Tantanapornkul *et al*[70] regarding prediction of IAN exposure. About the incidence of nerve injuries, there are no significant differences between the radiographic techniques. Only two cases of nerve damage are reported, one after CBCT-based planning and the other after PAN-based planning. However both cases reverted in 3 months.[6] This indicates that the nerve was not injured by the injection of local anaesthetic, which happens very rarely (0.0001% to 0.01%).[6,75,76] In order to create guidelines for the use of CBCT, more reviews based on various RCTs are needed.[6] Nonetheless, Flygare and Öhman[77], and Sanmartí-Garcia *et al*[78] recommend the use of CBCT in cases where PAN reveals a close relation between the tooth and the IAN canal (Figure 10).[6]

Figure 10: Intimate relationship between the IAN and the roots of the tooth 38 (Panoramic radiograph). *IN* Gay-Escoda C. Tratado de Cirurgía Bucal - Tomo I. Madrid: Ediciones Ergón, SA; 2004. 170–408 p.[43]

5.6. Vitamin D3 supplementation

Considering patient's health in this matter of third molar surgical extractions, Oteri *et al*[14] thought about the importance of vitamin D3 supplementation in patients with low levels of vitamin D3, and how supplementation before the procedure would affect postoperative complications. Vitamin D3 is a prohormone that can be synthetised by the skin through exposure to ultraviolet rays, by irradiation of 7-dehydrocholesterol, or obtained from dietary sources. This molecule is then transformed into other molecules in the liver and kidneys in order to become active.[14] It is also an essential nutrient[14,79] crucial in bone metabolism.[14] The hormonal form of this vitamin has an important role in calcium and phosphate absorption, regulates the immune system[14,80] and functions as a modulator, decreasing the prostaglandins secretion, which benefits immunity.[14] In this study, the metabolite "25(OH)D", that circulates in the blood stream is measured to recognize whether the patients have low levels of vitamin D3 or not. The patients showing vitamin D3 blood levels ≤30 ng/mL are recruited. Finally, Oteri *et al*[14] find that higher levels of vitamin D3 are beneficial in reducing oedema and also pro-inflammatory biochemical factors, such as tumour necrosis factor-alpha, Interleukin-1-beta and Interleukin-6. This expedites the healing process due to reduced inflammatory response. Even though the pain scores did not show significant differences, it is known that vitamin D3 is crucial in bone formation and mineralization, which leads to a better healing process and comfortable postoperative period.[14] Due to these interesting results, and since this is the only existing study addressing the relation between vitamin D3 and third molar extractions, there is a great need for new studies on this topic.

5.7. Mucoperiosteal flap designs

Mucoperiosteal flap designs are important in a procedure such as third molar surgery, because they determine the duration of the healing process, feasibility of primary closure, they provide appropriate atraumatic access to the surgical site and also influence postoperative complications.[81] However, it is known that raising a flap can cause trauma to the underlying bone, yet there is a lack of consensus on whether there are actually significant differences, at least regarding mandibular third molar surgery.[7,82] There are many types of flap designs[9,57,81] and the operator must know their features in order to

choose the most adequate design and minimize the patient's discomfort and prevent complications.[7,30,83–85] The most used are triangular and envelope flap designs[9,55,82] that are compared in one of the selected studies.[7] Along with mucoperiosteal flap designs, the use of surgical drains and different wound closure techniques are also ways of minimizing postoperative complications.[9,20,30,55,83,86]

In surgical procedures, when performing an incision, it is beneficial to place it in sound bone and not on the extraction socket. Even though this is very common, it is not advisable because it influences healing of the mucosa, and in some cases wound dehiscence and subsequent secondary wound healing may occur.[9] When this happens, the flap usually heals in a more buccally position, which leaves the socket unprotected and promotes food impaction, postoperative infections, delayed healing and may influence the probing depth on the distal aspect of the mandibular second molar.[9,87,88] Other than this, secondary healing can occur when using surgical drains, in mucosal excision, single interrupted suture or suture-less technique.[9,88] Regarding periodontal probing depth, besides what is mentioned above, there appears to be a subpopulation of individuals that have a higher risk for periodontal defects after an extraction, such as age over 26 years old, pre-existing periodontal defects (clinical attachment loss - CAL > 3 mm or periodontal pockets > 5 mm) and a horizontal[13] or mesioangular impaction.[13,89] Therefore, in order to prevent secondary healing and further periodontal defects, the operator can prioritize one of the flap designs that are less prone to this, such as the comma-shaped flap, the tongue-shaped flap or the lingually based triangular flap,[9,30] and choose to suture the oral mucosa[9,88] with the horizontal mattress suture technique,[1] for example. However, there is some controversy regarding the most advantageous type of healing.[5] Some authors actually find secondary healing more beneficial because it facilitates drainage, which reduces oedema.[5,35,90–94]

According to Bhargava *et al*[81], the flap must be created with the intent to remove the mucosa from the surgical site in a passive way, so it is possible to place retractors and still have visibility and enough space for tooth extraction. If this is properly attained, the difficulty of the procedure decreases.[81]

Yolcu and Acar[9], that compares triangular and lingually based triangular flap designs (Figure 11), finds no significant differences between oedema, trismus and wound healing.

Only pain scores show a significant difference between flap designs, with a greater reduction when using the commonly known triangular flap design. Nonetheless, they notice that when using the lingually based triangular flap design there is less wound dehiscence, even though this result is not statistically different. Yolcu and Acar[9] believe that the new lingually based flap design is a promising alternative to other flap designs, especially because the distal incision does not lie on the extraction socket.[9] Since this is the first study mentioning this new flap design, more studies are needed with a larger sample size and with different comparisons.

Another Baqain *et al*[7], that studies the changes of several postoperative complications based on two different mucoperiosteal flaps, finds that triangular flap design is more effective when considering the changes in periodontal probing depth on the distal aspect of the mandibular second molar, when compared to envelope flap design (Figure 12). Yet, envelope flap design shows a reduced incidence of oedema and trismus, specifically in days 2nd and 7th, and 14th, respectively. All these findings are statistically significant.[7] In this study, Baqain *et al*[7] state that triangular flap design might have a greater incidence of oedema and trismus due to inflammation of the muscles of mastication.[7,95] This increased inflammation is most likely caused by the anterior releasing incision.[7] However, other authors do not find significant differences between both flap designs, claiming the flaps are very similar.[7,30,82,96,97] Other parameters studied by Baqain *et al*[7], such as pain, plaque index, bleeding on probing, wound dehiscence, did not show a significant difference between flap designs. In regard to infections and alveolar osteitis, there were no reported cases. This should be interpreted with caution due to the small sample size in this study.[7] Ultimately, to choose from one of these flap designs, the operator should evaluate each case scenario and consider especially the patient's oral hygiene.[7,98] Given that envelope flaps have a greater tendency to increase the probing depth on the distal aspect of the mandibular second molar, this type of flap design is not as suitable for patients with poor oral hygiene.

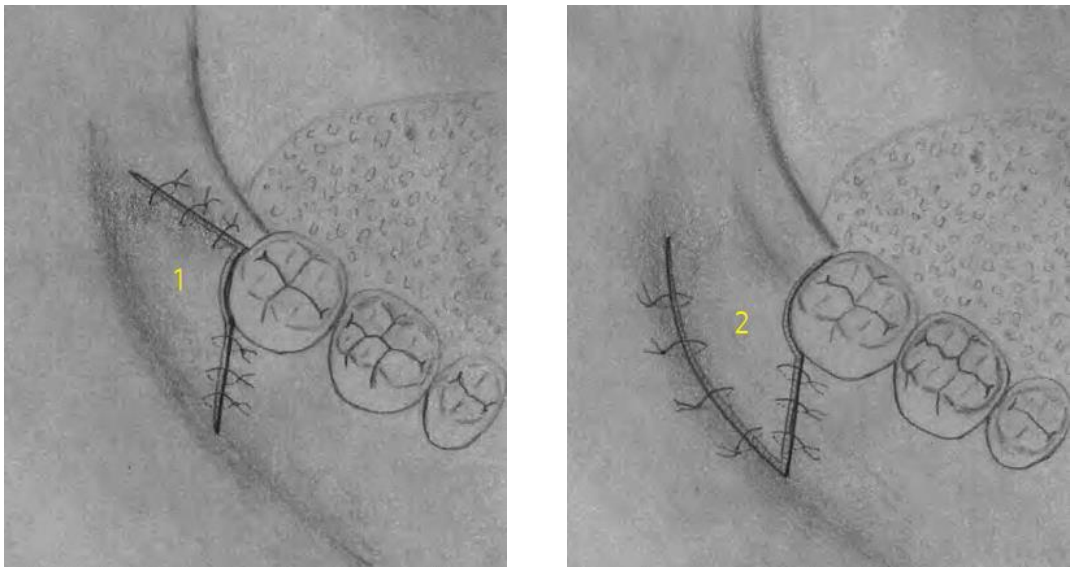

Figure 11: Mucoperiosteal flap designs. 1 - Buccaly based triangular flap, 2 - Lingually based triangular flap. *IN* Yolcu U, Acar AH. Comparison of a new flap design with the routinely used triangular flap design in third molar surgery. Int J Oral Maxillofac Surg. 2015;44(11):1390–7.[9]

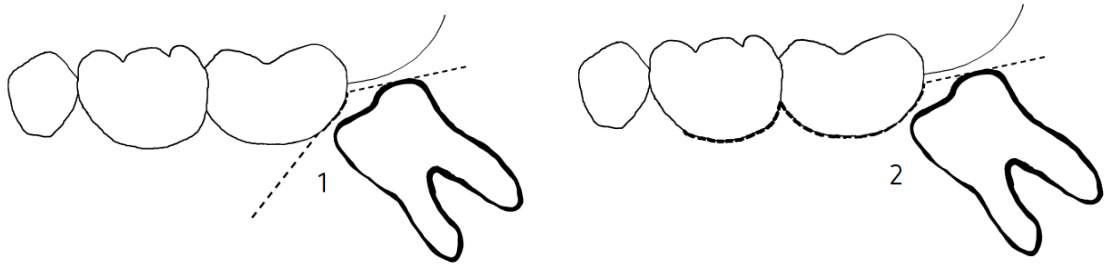

Figure 12: Incisions for the mucoperiosteal flap designs. 1 - Triangular flap, 2 - Envelope flap. *IN* Baqain ZH, Al-Shafii A, Hamdan AA, Sawair FA. Flap design and mandibular third molar surgery: A split mouth randomized clinical study. Int J Oral Maxillofac Surg. 2012;41(8):1020–4.[7]

5.8. Types of irrigating solutions

Irrigating solutions are very important during a surgical procedure that involves ostectomy, such as the extraction of an impacted tooth. This prevents bone injuries, improves the capacity to properly visualize the working field by the operator[2,15,99] and avoids tissue overheating.[2] Different types of cleansing solutions can be used.[2,15] Examples are: sterile

water,[2] ozonized water,[2] normal saline,[2,15] chlorhexidine,[2,9,100] povidone iodine,[15] sodium hypochlorite, hydrogen peroxide.[2,100]

One of the most used and recommended is normal saline since it is isotonic, and it has similar properties to the tissue fluid.[2,15,101] Glória *et al*[2], that test the effect of ozonized water and double distilled water (sterile water) as irrigating solutions, choose distilled water as a control due to the following valued reasons: availability, low cost, non-toxic, non-haemolytic and antiseptic. This indicates that double distilled water is also a great choice as an irrigant. Regarding ozone therapy, it has antimicrobial and anti-inflammatory properties against bacteria, viruses and fungi, which is beneficial in controlling a possible infection.[2,101] It is a good treatment option due to its advantages: it can be easily manipulated, tolerable by patients, does not have side effects[2] can accelerate the healing process of the soft tissues present in the oral cavity, especially in the beginning stage after an extraction,[2,35] and it produces less cytotoxicity than ozone gas, chlorhexidine (0.2 and 2%), sodium hypochlorite (2.25 and 5.25%) and hydrogen peroxide (3%).[2,100] However, this study shows no significant differences in the postoperative complications studied between the test and control groups. Since, according to this study, ozonized water and double distilled water obtain similar results, both irrigation techniques can be considered comparable, at least regarding the control of postoperative complications such as oedema, trismus and pain.[2] Concerning previous studies, some authors testing ozone therapy through gel, which is used topically after an extraction, did not find a significant reduction of oedema and trismus.[2,35] Nonetheless, ozonized gel can be applied twice a day for 3 days and it decreases oedema, trismus and pain, as Prasad *et al*[102] claim.[2,102] According to Patel and Gujjari[103], ozone therapy should be applied after the surgical procedure, when inflammation rises for it to be most effective.[2,103] Also Xu and Wu[104] state that pH, temperature and contact time are important details that can influence the efficacy of this therapy.[2,104] Since Glória *et al*[2] use ozone water as an irrigant, which is constantly being suctioned, the contact time with the oral tissues is very limited. Furthermore, as this method only includes irrigation during the procedure and not postoperatively, and the inflammation peak has not been reached yet at that point, these factors may explain the results of Glória *et al*[2]. Nevertheless, as the use of ozonized water in oral surgical procedures is still quite new, these findings need to be interpreted with caution.[2]

Jadhao *et al*[15] test normal saline, chlorhexidine and povidone iodine to evaluate the possible decrease of postoperative complications. Some of the advantages of chlorhexidine are: an effective antiseptic,[15,99] fast-acting and residual effect over 48h.[15] In regard to povidone iodine, it is a broad-spectrum microbial agent against bacteria, viruses and fungi, and it is also fast-acting.[15,105] The results of this study are very clear, showing a greater reduction in all postoperative complications, with a significant difference ($p < 0.01$) in most of the complications when comparing normal saline and povidone iodine with chlorhexidine, being chlorhexidine the most effective irrigating solution. The parameters evaluated with significant differences are oedema (on the 1st postoperative day), trismus, pain and alveolar osteitis.[15] Specifically alveolar osteitis, which accounts for 25 to 30% of the cases, as well as infections, are the most common postoperative complications related to this surgical procedure.[15,87] The complications that did not show a significant difference, but that were still greater with normal saline and povidone iodine, are oedema (on the 7th postoperative day), infection and food impaction.[15] Other authors also corroborate these findings, stating that chlorhexidine prevents pain and alveolar osteitis more effectively than povidone iodine,[15] and that the use of chlorhexidine decreases alveolar osteitis very intensely.[15,106] Curiously, in this study none of the patients were identified with alveolar osteitis when using chlorhexidine.[15]

5.9. The use of platelet-rich fibrin

Platelet-rich fibrin (PRF) or leukocyte platelet-rich fibrin (L-PRF), normally used interchangeably, is an additive-free biomaterial[4] composed of autologous platelets, growth factors, glucan chains, glycoproteins, cytokines and leukocytes that when combined can synthesise an extracellular fibrin matrix.[3,4,107,108] It enables chemotaxis, cell proliferation and differentiation[3,4,107,109,110] (including osteoblasts and fibroblasts),[109,111] and angiogenesis.[3,4,107,109,110]

All these features are crucial in tissue regeneration.[3,4] Studies indicating that there is actually a reduction in postoperative complications after third molar extraction when using PRF are still scarce,[13] nonetheless, this technique has become increasingly interesting due to the PRF's healing potential.[3,4]

The process of creating PRF is carried out by centrifuging the patient's own blood without any anticoagulant.[3,4] Centrifugation should be performed at the indicated speed to include within the clot all cells of interest.[3] The selected studies used the following centrifugation speeds: 1500 rpm,[3] 2800 rpm[4] and 3000 rpm.[3,13] When this procedure is performed, the cells position themselves within the tube according to their density. The fibrin clot mixed with platelets, leukocytes and growth factors stand in the centre of the tube, between red blood cells located at the bottom, and plasma at the top of the tube.[4,108] Since what is needed is just the aggregate located in the middle of the tube, red blood cells and plasma are discarded.[4]

PRF is considered the second generation of platelet-rich plasma (PRP), that unlike PRF, is composed of platelets and plasma.[3,4,13,108] PRP has been studied specifically in this application for over two decades,[4] however, the authors often find that its healing potential is not very high compared to PRF.[13,61,108,112–114] This may explain the recent interest in analysing the use of L-PRF and advanced platelet-rich fibrin (A -PRF) as a way to prevent complications in third molar extractions.[3] The difference between L-PRF and A-PRF is that the latter contains a greater amount of leukocytes, which can be attained by reducing the g-force during centrifugation.[3,115] This can be very beneficial, because white blood cells have the ability to attract mediators and other cells that allow for a better healing process.[3,116,117]

According to the study of Kobayashi *et al*[118], the results show a significant difference between A-PRF and L-PRF when focusing on the release of growth factors, exhibiting a higher value in the case of A-PRF.[3,118] Since the use of A-PRF seems very promising, Caymaz and Uyanık[3] decide to compare the effect of A-PRF and L-PRF application on postoperative complications. They find that A-PRF is more effective in reducing pain and the number of analgesics taken by the patients.[3,119] Nonetheless, Caymaz and Uyanık[3] do not find any statistically differences in oedema and trismus. Kumar *et al*[13] and Daugela *et al*[4], that study the influence of L-PRF, find that when applied, it reduces oedema and pain. However, Kumar *et al*[13] also find a significant difference in the reduction of trismus and periodontal probing depth. Regarding bone formation, Kumar *et al*[13] could not find a significant difference, even though the values were higher when using L-PRF. On the other hand, Daugela *et al*[4] find a significant wound healing improvement when using L-PRF, and only

come across positive cases of alveolar osteitis without the use of L-PRF. This result is very encouraging and optimistic, since alveolar osteitis is the most common postoperative complication after third molar surgery.[4,120]

In a previous systematic review, Fabbro *et al*[121] claim that various authors have this similar perspective regarding the benefits of using PRF.[13,121] However, because there is a lack of standardization of the technique, more studies with a longer period and larger sample size are needed to evaluate the true regenerative effects.[13,121]

5.10. Primary and secondary healing

Wound closure can be primary or secondary.[9,52] In primary wound healing or primary closure, the mucoperiosteal flaps are sutured in order to close the gap between them, completely covering the extraction socket.[9,94] In secondary wound healing or secondary closure, the extraction site remains uncovered in communication with the oral cavity.[94]

As mentioned above, some operators prioritize primary healing[94] and others prioritize secondary healing.[5,35,90–94] Only few studies report no differences between both healing types.[5,94] Some reasons for recommending secondary healing are: it facilitates drainage of inflammatory products,[5,9,94] decreases postoperative pain and decreases oedema.[9] And factors favouring primary healing are: less chances of food impaction, less likelihood of infections,[5,9] and faster wound healing.[9]

The results of Pachipulusu and Manjula[5] favour secondary healing over primary healing, particularly in relation to pain, oedema, and trismus. The only parameter where significant differences are not find is periodontal probing depth, which indicates that the healing types do not influence periodontal healing.[5] Other authors also have similar results regarding pain, oedema,[5,35,90,122] and trismus.[122] Unlike one of these studies[90], Pachipulusu and Manjula[5] only find one case of alveolar osteitis in secondary closure, while Pasqualini *et al*[90] report a higher incidence in primary closure. These differences may be due to the sample size, since Pachipulusu and Manjula[5] only study sixty cases compared to Pasqualini *et al*[90] that study two hundred cases.

5.11. Suture techniques

The most frequently used medical device for wound closure are sutures.[123] Regarding suture materials, they can be resorbable or nonresorbable, and usually in third molar extractions, resorbable thread is preferred.[1] Although, choosing nonresorbable thread can also be beneficial due to the haemostasis conferred.[1,9,94,124] Ultimately, there is no evidence on which suture material is the most adequate.[1]

About the type of thread, there are monofilament and multifilament sutures. It is advantageous to use monofilament thread due to less dental plaque aggregation, which significantly reduces inflammation around the sutures when compared with multifilament thread (Figure 13). Besides, it can reduce postoperative pain. There is also another way of categorising sutures, which is through their origin, in particular, natural or synthetic sutures. Considering wound healing, synthetic thread types exhibit a better healing response compared to natural thread types.[123] Therefore, according to Dragovic *et al*[123], it is preferable to use synthetic monofilament sutures in oral surgical procedures.

The selected studies in this integrative review use silk (natural or synthetic nonresorbable multifilament),[1,2,5,7,13,14] polyglactin (synthetic resorbable multifilament),[4,5] plain gut (natural resorbable multifilament)[9] and nylon sutures (synthetic nonresorbable monofilament).[15] One of the studies does not specify the type of suture used,[3] and two more studies do not mention any type of suturing technique.[6,8]

Regarding wound healing types, even though in the literature, some authors claim that secondary healing is more advantageous for the patient because it reduces complications, such as oedema, pain[94] and inflammatory postoperative response;[71] primary wound closure is still important especially in cases where the patients are taken bisphosphonates, immunosuppressant drugs or undergoing radiotherapy.[1,9] Because these patients are immunosuppressed, delayed primary closure may result in alveolar osteitis, infections, osteomyelitis,[9] osteoradionecrosis and medication-related osteonecrosis.[1] Furthermore, some complications can also arise in systemically healthy patients, such as alveolar osteitis, food impaction and periodontal defects.[1,9,125]

The type of suturing technique chosen among different operators can differ, whether in third molar extractions or any other type of surgical procedure in the oral cavity.[5]

However, there is a preference for simple interrupted suturing technique.[1] Because of the importance in understanding the impact of suturing techniques in postoperative complications, in 2017 Acar *et al*[1] decide to compare the most commonly used technique with horizontal mattress suturing. They investigate how both suturing techniques influence oedema, trismus, pain, and especially wound healing.[1] In the protocol, Acar *et al*[1] use triangular flap design and choose to leave a gap on its vertical incision, because it has been shown that this can help drainage and thus reduce the postoperative complications.[1,83] They notice that horizontal mattress sutures are more effective than simple interrupted sutures considering primary wound healing, even though the levels of pain, trismus, and oedema do not significantly differ between techniques. According to Acar *et al*[1], this may be explained by the usage of the triangular flap design with the gap on the vertical incision.

Since there is a focus on healthy patients in this study, further studies are needed to evaluate how these suturing techniques may influence postoperative complications in immunosuppressed patients.

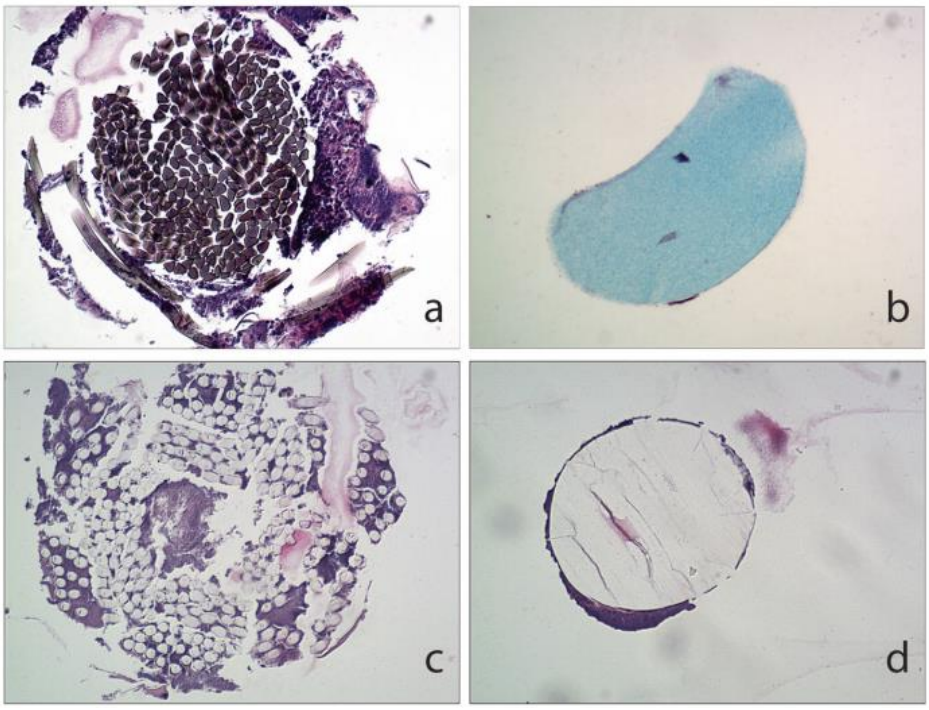

Figure 13: Microscopic samples of multi and monofilament sutures. Greater amount of inflammatory cells around multifilament sutures (a, c) and absence of inflammatory cells around monofilament sutures (b, d). *IN* Dragovic M, Pejovic M, Stepic J, Colic S, Dozic B, Dragovic S, et al. Comparison of four different suture materials in respect to oral wound healing, microbial colonization, tissue reaction and clinical features—randomized clinical study. Clin Oral Investig. 2020;24(4):1527–41.[123]

5.12. The influence of acupuncture

One of the complications that has not been addressed is anxiety. Anxiety is an emotional state characterized by fear, pain or phobia, normally linked to third molar extractions that affects the patient psychologically and psychosomatically.[8] When anxious, the patients may suffer from tremors, arrhythmias, vasovagal reactions, and in some cases, dental treatment may not be possible to perform.[8,126]

The anxiety state of patients influences not just the preoperative and the intraoperative periods, but the postoperative period as well, by increasing the magnitude of the complications.[8,127,128] These complications can be prevented to some degree with the use of drug therapies,[8,129,130] nonetheless, in order to avoid overuse of medicines and reduce side effects, acupuncture can be used as a safe and effective alternative therapy.[8,131] Some studies recommend the use of acupuncture as a means to reduce oedema,[132] trismus, pain[8] and anxiety.[128,133]

Armond *et al*[8] decide to evaluate these variables using the concept of active needle versus placebo needle, since the majority of studies that have been addressing this topic do not make this comparison. The term active needle refers to acupuncture therapy, while placebo needle is considered to be the absence of treatment (Figure 14). Overall, they find that the control of oedema achieves better results with the use of active needles compared to placebo acupuncture. Armond *et al*[8] attribute this result to the increase in cortisol levels caused by acupuncture. Nonetheless, they find no significant differences in trismus, pain, anxiety levels and the number of analgesics taken by the patients.[8] Vase *et al*[134] and Lao *et al*[135], studying the same topic, find lower pain values in the active protocol compared to the absence of treatment.[134,135] However, a meta-analysis shows that acupuncture has a reduced effect specifically on postoperative pain compared to placebo acupuncture.[136] Regarding anxiety, according to previous studies[8,128], the true effects of acupuncture remain controversial. When comparing acupuncture therapy to an untreated group, it seems effective, but when compared to placebo, there is a great reduction in the treatment effect.[8,128] This may suggest the existence of a placebo effect of acupuncture,[137,138] which is a major limitation of this study.

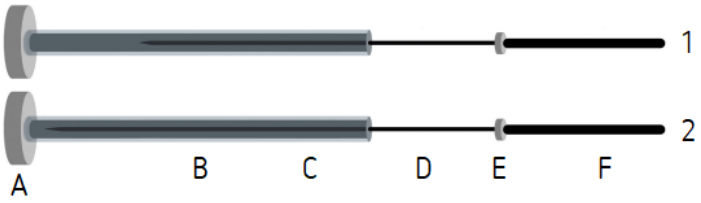

Figure 14: Placebo needle (1) and Active needle (2). A - Adhesive pedestal, B - Opaque guide tube, C - Silicone stuffing, D - Needle body, E - Stopper, F - Needle handle. *IN* Armond ACV, Glória JCR, dos Santos CRR, Galo R, Falci SGM. Acupuncture on anxiety and inflammatory events following surgery of mandibular third molars: a split-mouth, randomized, triple-blind clinical trial. Int J Oral Maxillofac Surg. 2019;48(2):274–81.[8]

5.13. Additional information / limitations

Some parameters that are analysed in the studies, such as age,[2–5,13,14] gender[2,4,9,13,14] of patients, and operative time[1–3,7–9] are not mentioned in this integrative review, as none of the studies report significant differences between the groups tested.

Most of the selected articles only focus on the extraction of mandibular third molars.[1–9,14,15] More studies should be carried out in order to increase the amount of information available about postoperative complications in maxillary third molars.

Some authors prescribe medications as part of the protocol.[1,3–5,7–9,13,15] Although there is no comparison on the effectiveness of these drugs, since other studies do not use any active ingredient[2,6,14] or may use a different drug therapy, the studies cannot be compared linearly.

Regarding *p* values, not all authors use the same method. Most consider a parameter to be statistically significant when the value is lower than 0,05.[1–9,13,15] In contrast, some studies use *p* values of 0.01[3,4,7,13–15] or even 0.001.[5] Due to this, the results need to be interpreted with caution.

6. CONCLUSION

In order to prevent postoperative complications associated with impacted third molars without using drug therapies, among the techniques reviewed, the most efficient methods sorted in descending order are:

- Preference for secondary closure, due to its ability to significantly reduce oedema, pain (*p* value < 0,001) and trismus (*p* value < 0,002). It is especially indicated when the patient has good oral hygiene and is not immunosuppressed, and also advisable when the patient does not present deep periodontal probing depth on the distal aspect of the second molar preoperatively. In these cases, primary closure is preferable;

- The use of chlorhexidine as an irrigant, which is more beneficial than the most used irrigant (normal saline) when it comes to oedema, trismus, pain and alveolar osteitis (*p* value < 0,01);

- The use of A-PRF, this biomaterial can reduce pain and the number of analgesics taken by the patients when compared to L-PRF (*p* value < 0,05). However, L-PRF is also effective in reducing oedema, trismus, pain, periodontal probing depth (*p* value < 0,05), alveolar osteitis and improving healing (*p* value < 0,01), when compared to its absence;

- The use of envelope flap design, that obtains better results considering oedema and trismus (*p* value < 0,05) when compared to triangular flap design, which in turn is more effective in reducing periodontal probing depth (*p* value < 0,01);

- The use of horizontal mattress sutures, due to lower likelihood of wound dehiscence compared to simple interrupted sutures, when using triangular flap design (*p* value < 0,05). Besides, it is important to leave a gap on the vertical incision for drainage;

- The use of CBTC versus PAN, which is preferable in predicting nerve exposure (*p* value < 0,05). There are no guidelines for its use, nonetheless, it is recommended if the third molar root overlaps the IAN when using PAN.

There are also benefits in taking vitamin D3 supplements in case of deficiency. Yet, further studies are needed to better understand its influence, especially in healthy patients. Regarding anxiety control with acupuncture, there is conflicting information about its effectiveness due to a possible placebo effect.

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