

How to Cite:

Menon, V. D., & Muthusekhar, M. R. (2022). Comparison of proteolytic enzymes vs corticosteroids in preventing postoperative sequelae in mandibular third surgery: A systematic review. *International Journal of Health Sciences*, 6(S3), 6470–6490. <https://doi.org/10.53730/ijhs.v6nS3.7450>

Comparison of proteolytic enzymes vs corticosteroids in preventing postoperative sequelae in mandibular third surgery: A systematic review

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Abstract--Third molar removal is the most frequently done procedure. Pain, swelling, trismus, alveolar osteitis are the most common postoperative complications. Few authors have used certain drugs like corticosteroids and proteolytic enzymes in order to reduce the postoperative complications. The aim of this systematic review is to evaluate in an evidence based way, the effectiveness of oral proteolytic enzymes and corticosteroids in controlling postoperative complications following mandibular third molar surgery. The objective of this systematic review is to compare the effectiveness of oral proteolytic enzymes and corticosteroids in preventing postoperative sequelae following mandibular third molar surgery. The Databases of PubMed, Cochrane and Google scholar were searched for the related topics along with a complimentary manual search of all oral surgery journals till December 2020. Four articles were selected based on the inclusion criteria. One among the four clinical trials comparing oral proteolytic enzymes and corticosteroids, they show significant differences proving post-operative swelling and trismus are less in patients receiving oral proteolytic enzymes compared to corticosteroids. In the other three trials patients receiving corticosteroids showed decreased post-operative swelling compared to oral proteolytic enzymes. Number of good quality randomized controlled trials included are very limited, from the above results we can conclude that corticosteroids are more effective in reducing swelling post third molar surgery. Properly

designed randomized clinical trials are needed to evaluate the effectiveness of oral proteolytic enzymes in reducing post operative swelling following third molar surgery.

Keywords---pain, inflammation, impaction, enzymes, steroids.

Introduction

The most common intervention in oral and maxillofacial surgery is the lower third molar extraction. The mandibular third molar is the most commonly affected tooth in the oral cavity(1). The frequency of the affected mandibular third molar is 41.13%, according to Kramer and Williams. The lack of space in the overlying alveolar arch is the predominant cause of eruption failure. Most of the patients are asymptomatic with impacted mandibular third molar. Some patients exhibit severe conditions such as cyst or neoplastic lesions in the underlying follicular tissue(2).In order to avoid these pathogenic complications, the removal of impacted third molars is necessary. The removal of the impacted third molar can cause the patient considerable postoperative discomfort. Swelling, pain, decreased mouth opening are the common postoperative complications. Oral surgeons have been using steroidal anti-inflammatory drugs (glucocorticoids), such as dexamethasone, to minimize these sequelae and have obtained satisfactory results(3).Parallel to glucocorticoids, the role of natural products as remedies has been recognized since ancient times. Natural products with anti-inflammatory activity have long been used as a folk remedy for inflammatory conditions such as fevers, pain, migraine, and arthritis(4). Proteolytic enzymes are, particularly effective in the treatment of soft tissue inflammations and traumas, in localized inflammations, especially in the presence of edema and also in postoperative tissue reactions(5) This review is to evaluate the effectiveness of oral proteolytic enzymes in preventing postoperative complications following mandibular third molar surgery. Previously our team has a rich experience in working on various research projects across multiple disciplines (6–20) Now the growing trend in this area motivated us to pursue this project.

Materials and Methods

Inclusion criteria

Criteria for considering studies for the Review

Types of studies

- Randomized controlled trials
- Clinical trials.

Types of Participants

Patients undergoing surgical removal of impacted lower third molar.

Types of Intervention

Post-operative swelling and mouth opening is evaluated after administration of oral proteolytic enzymes in lower third molar surgery.

Types of Comparison

Post-operative swelling and mouth opening is evaluated after administration of corticosteroids in lower third molar surgery.

Types of Outcome Measures

Post-operative swelling and mouth opening is evaluated following lower third molar surgery

Exclusion criteria

The following studies were excluded:

- Case reports / Case series
- Studies in which either oral proteolytic enzymes or corticosteroids are not used.
- Studies not involving surgical removal of impacted lower third molar

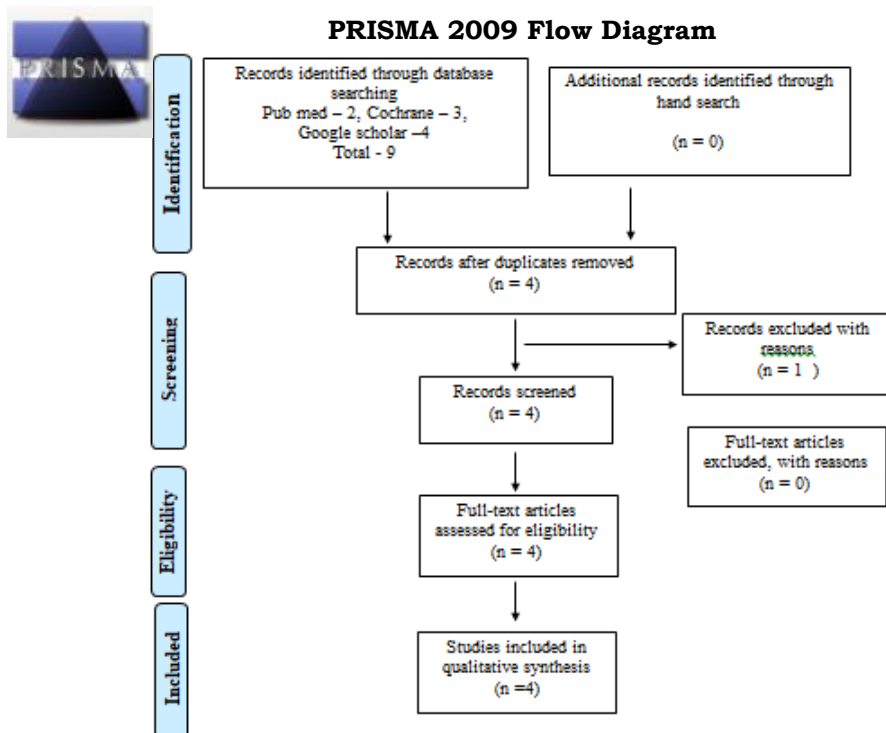
Sources used

The Databases of PubMed Advanced Search, Cochrane Database of Systematic Review and Google scholar were searched for the related topics.00. We used free-text terms to search the following journals”

- British Journal of Oral and Maxillofacial Surgery
- International Journal of Oral and Maxillofacial Surgery
- Journal of Oral and Maxillofacial Surgery
- Journal of Cranio Maxillofacial Surgery
- Quintessence International Journal

Only articles in English and human species were applied during the electronic search to include all the possible clinical trials that are relevant for the search phase of the systematic review. Reference lists of the identified randomized trials were also checked for possible additional studies.

Search Flow Chart



Data collection and analysis Screening and Selection

Electronic search was carried out using the keywords in the Search engines-PubMed, Cochrane and Google Scholar which yielded a total of nine articles. Based on pre-set inclusion and exclusion criteria, the titles of the studies identified from the search were assessed independently by two review authors (Dr.Vivek.D.Menon, Dr.Muthusekhar.M.R). Conflicts concerning inclusion of the studies were resolved by discussion. One article excluded after reading titles. Five titles were identified from the search after excluding four duplications. Abstracts of selected articles were reviewed independently. One article was excluded after reading the abstract. Full text articles were retrieved for 4 relevant studies. The reference list of the full text articles were reviewed for identifying additional studies. Titles of articles relevant to the review were selected by discussion. Difference of opinion concerning inclusion of a study was resolved by discussion and one article was eliminated after reviewing abstracts. Quality Assessment criteria to evaluate the studies were decided by two review authors in accordance with CONSORT guidelines. The risk of bias for each study was independently assessed by the review authors and conflicts concerning risk of bias were sorted by discussion.

Data Extraction

Data extraction for general characteristics of studies and variables of outcome was done. For each trial the following data were recorded:

- Author and Journal
- Study Design
- Sample Size
- Participants and Group
- Methodology
- Parameters
- Statistical Analysis
- Results

Table 1
Variables of interest

S.No	VARIABLES OF INTEREST
1.	Post-operative Swelling evaluated using facial measurements
2.	Post-operative Mouth opening evaluated measuring Interincisal distance

Quality assessment

(Higgins and Green. Cochrane reviewer's hand book 2009). The quality assessment of included trials was undertaken independently as a part of data extraction process. Four main quality criteria were examined.

- **Method of Randomization**, recorded as
 - a. YES- Adequate as described in the text
 - b. NO- Inadequate as described in the text
 - c. Unclear in the text
- **Allocation Concealment**, recorded as
 - a. YES- Adequate as described in the text
 - b. NO- Inadequate as described in the text
 - c. Unclear in the text
- **Outcome assessors Blinded to intervention**, recorded as
 - a. YES- Adequate as described in the text
 - b. NO- Inadequate as described in the text
 - c. Unclear in the text
- **Completeness of Follow up** (was there a clear explanation for withdrawals and dropouts in each treatment group) assessed as
 - a. YES- Dropouts were explained
 - b. NO- Dropouts were not explained
 - c. None- No Dropouts or withdrawals.

Other methodological criteria

Examined included:

- Presence or Absence of sample size calculation.
- Comparability of Groups at the start.
- Clear Inclusion or Exclusion criteria.
- Presence or Absence of estimate of measurement error.

Results

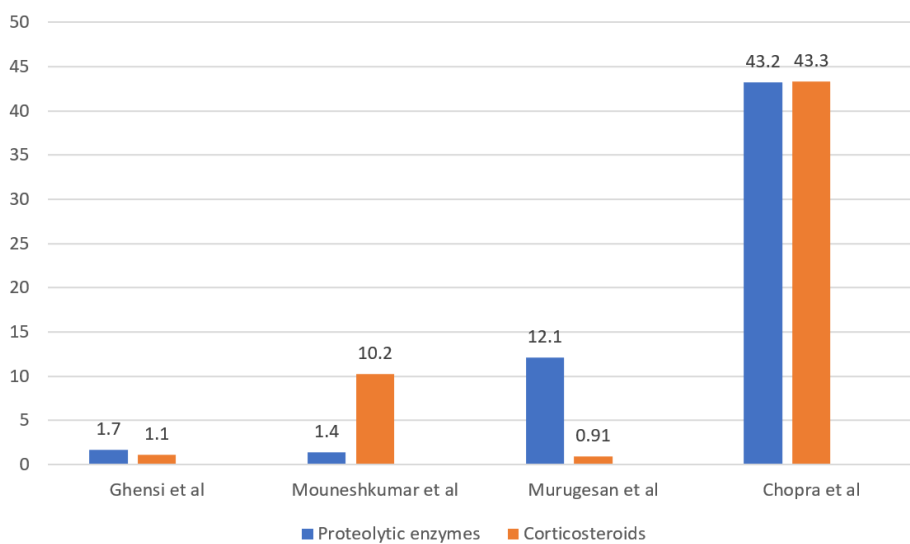
Table 2
Description table of included studies

S. No	Author	Year	Study design	Sample size	Age	Medication prescribed	Method of evaluation	Mean Values	Results
1	Ghensi et al	2017	Randomised controlled study	N=84	18 years and above	Bromelain, dexamethasone.	Swelling measured using 3 soft tissue points, Mouth opening was recorded by measuring interincisal distance	Facial Swelling Proteolytic enzyme group POD 2nd - 7.1 POD 7th - 1.7 Dexamethasone group POD 2nd- 3.2 POD 7th- 0.9 Mouth opening proteolytic enzyme group POD 2nd- 13.2 POD 7th- 3.3 Dexamethasone group POD	The facial swelling experienced in the dexamethasone group was significantly less than that experienced by the proteolytic enzyme group. No statistically significant change in trismus between the groups.

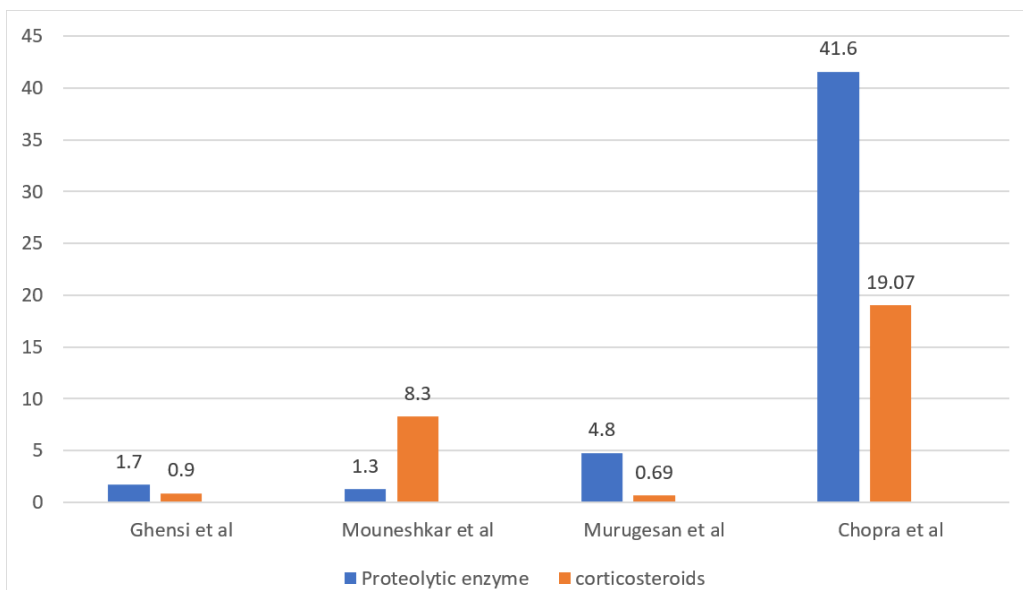
								2nd-13 POD 7th-3.1	
2	Moune shkum ar et al	2015	Rando mised contro lled trial.	N=100	not menti oned	Methylpre dnisolone and serratiope ptidase	Swelling measured using 5 soft tissue points, and Mouth opening was recorded by measuring Interincisa l distance.	Swelling Methylpr ednisolo ne group POD 1st 36.4 POD 3rd 26.8 POD 5th 10.2 Serratiop eptidase Group- POD 1st 37.7 POD 2nd 16.8 POD 3rd 1.4 TRISMU S Methylpr ednisolo ne Group POD 1st 17.7 POD 3rd 9.4 POD 5th 1.3 Serratiop eptidase group POD 1st 22.1 POD 3rd 13.8 POD 5th 8.3	Swelling results were statistically insignificant between groups 1 and 2 on POD 1 and 3, statistical significance was observed on POD 5. Thus serratiopept idase has better efficacy in controlling post op edema than methylpred nisolone. The results showed statistical significance when compared between group 1 and 2. Resolution of trismus was better in group 2 compared to group 1. Hence serratiopept idase is better than methylpred nisolone in

									resolving trismus.
3	Murugesan et al	2012	Randomized controlled trial	N=110	not mentioned	serratiopeptidase group and dexamethasone group	Swelling measured using 7 point measurement method, and Mouth opening was recorded by measuring the Interincisal distance.	Swelling Serratiopeptidase group POD 1st 25.45 POD 3rd 20.26 POD 5th 13.67 POD 7th 12.12 Dexamethasone group POD 1st 13.41 POD 3rd 8.2 POD 5th 1.63 POD 7th 0.091 Trismus Serratiopeptidase group POD 1st 3.5 POD 3rd 3.9 POD 5th 4.5 POD 7th 4.8 Dexamethasone group POD 1st 1.3 POD 3rd 1.19 POD 5th 0.86 POD 7th 0.69	swelling was significantly reduced in the dexamethasone group compared to serratiopeptidase group, which was statistically significant on 7th day. Trismus both the drugs were equally ineffective in relieving trismus.

4	Chopra et al	2008	Randomised controlled trial	N=150	18-45 years	Serratiopeptidase group and betamethasone group	Swelling measured using 4 soft tissue points and Mouth opening was recorded by measuring Interincisal distance.	Swelling Serratiopeptidase group POD 1st-45.2 POD 3rd-44.1 POD 5th-43.4 POD 7th-43.23 Betamethasone group POD 1st-44.68 POD 3rd-43.92 POD 5th-43.54 POD 7th-43.37 Mean Mouth opening Serratiopeptidase group POD 3rd-52.71 POD 5th-41.65 Betamethasone group POD 3rd-31.83 POD 5th-19.07	betamethasone There was a significant difference between the drain and without drain group in swelling. There was significant difference between drain and no drain group in relation to mouth opening.
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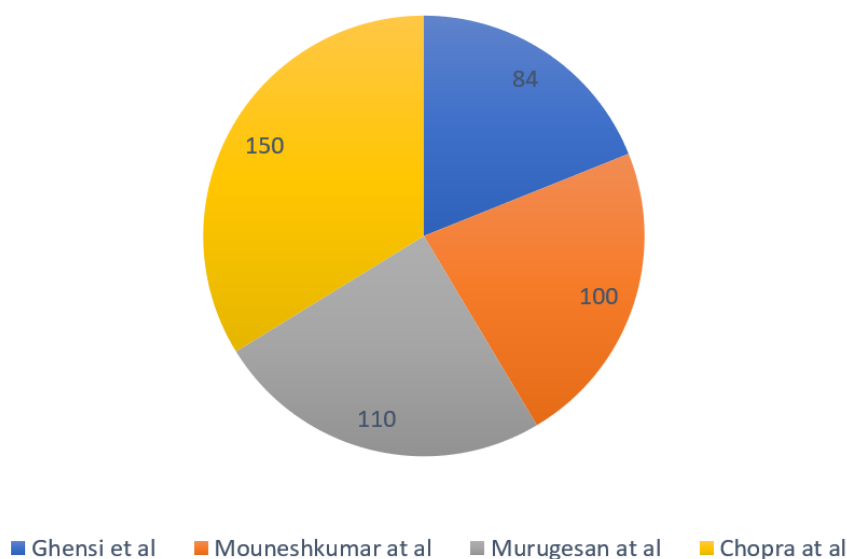


Graph 1. Comparison of post-operative swelling



Graph 2. Comparison of post-operative mouth opening

Sample Size



Graph 3. Comparison of sample size

Table 3
Evidence level of selected articles

(Based on Oxford Centre of evidence based medicine – Levels of Evidence March 2009)

Sl no	Author & Year	Study Design	Level of Evidence
1	Ghensi et al 2017	Randomised controlled trial	1b
2	Mouneshkumar et al 2015	Randomised controlled trial	1b
3	Murugesan et al 2012	Randomized controlled trial	1b
4	Chopra et al 2008	Randomised controlled trial	1b

Risk of bias in included studies

The study was assessed to have a “High risk” of bias if it did not record a “Yes” in three or more of the four main categories, “Moderate Risk” if two out of four categories did not record a “Yes”, and “Low Risk” if all the four categories recorded if randomization assessor, Blinding and Completeness of follow up were considered Adequate. In case of non-randomized and clinical trials without control group, it is recorded as Not applicable.

Table 4
Risk of bias- major criteria

S.No	Study	Randomization	Allocation concealment	Assessor Blinded	Drop outs described	RISK OF BIAS
1	Ghensi et al	NO	NO	YES	YES	MODERATE
2.	Mouneshkumar et al	NO	NO	NO	NONE	HIGH
3.	Murugesan et al	NO	NO	NO	NONE	HIGH
4.	Chopra et al	YES	YES	YES	NONE	LOW

Table 5
Risk of bias- minor criteria

S.No	Study	Sample justified	Baseline comparison	I/ E criteria	Method of error
1	Ghensi et al	NO	YES	YES	NO
2	Mouneshkumar et al	NO	YES	YES	NO
3	Murugesan et al	NO	YES	YES	NO
4	Chopra et al	YES	YES	YES	NO

Table 6
Summation table for individual parameters

S.No	Author	Year	Evaluation period	Outcome
1.	Ghensi et al	2017	2 nd and 7 th POD	Swelling – There was no significant difference in swelling between the groups, Results showed an increased reduction in swelling with combination of both proteolytic enzyme(bromelain) and dexamethasone. Mouth opening – There is no statistically significant difference between the groups in trismus.
2.	Mouneshku	2015	1st ,3rd and 5th POD	Swelling –

	mar et al			There was a statistically significant difference between the groups in swelling, Results favour proteolytic enzyme group(Serratiopeptidase) Mouth opening – There was a statistically significant difference between the two groups in trismus.Proteolytic enzyme(Serratiopeptidase) showed better results in resolving trismus compared to methylprednisolone.
3.	Murugesan et al	2012	1 st , 3rd , 5th and 7th POD	.Swelling – There was a statistically significant difference between the groups in swelling in favour of the dexamethasone group. Mouth opening – There was no statistically significant difference between the groups in trismus.
4.	Chopra et al	2008	1st , 3rd , 5th and 7th POD	Swelling – There was a statistically significant difference between the groups in swelling in favour of the Betamethasone group. Mouth opening – There was a statistically significant difference between the groups in mouth opening in favour of Betamethasone group.

Discussion

Many of the surgeries in the third molar are done without more severe complications. Anyhow, there may be some severe complications to the patient such as swelling, dysphagia(21) , alveolar osteitis, infection, periodontal pocketing ,postoperative pain, trismus, bleeding, nerve injury, and delayed healing(22). Generally, they are considered as short-term consequences of the surgery in the

third molar; at the same time, they are supposed to cause damage to job disruption and quality of life. Tissue damage and inflammatory response are rare but serious complications associated with a number of dental procedures (23).

The frequency with which third molar extraction is performed leads inevitably to an increased risk of damage to nerve structures. Acute edema and postoperative pain can occur as a result of surgical procedure particularly the inflammatory process is an early and immediate reaction to injury (24). Some other causes are patient's gender and age, oral hygiene, administration of postoperative or preoperative medications, patients willingness to follow postoperative instructions, the presence of earlier periapical or periodontal pathology and structural and functional elements like surgery duration, osteotomy magnitude and surgical difficulty(25). The rate of complication for extraction of the third molar may vary within 2.6 and 30.9 % (11).

Previous research evaluating the effectiveness of corticosteroids after third-molar surgery have resulted in conflicting results. It is possible to attribute these variations to Different drugs, doses, routes of administration, methods of swelling assessment and the duration of the time for postoperative observation. Corticosteroids are mainly used after surgical procedures for suppressing tissue mediators of inflammation, thereby reducing transudation of fluids and decreasing edema. Although some reduction of postoperative pain generally accompanies a reduction of edema, steroids alone do not have a clinically significant analgesic effect(26). Among the natural products available on the market, bromelain, a mixture of proteolytic enzymes, is indicated by the pharmaceutical industry in general for all edematous conditions and/or inflammatory diseases involving soft tissues, including surgical tooth extractions. To date, however, only 5 indexed studies, evaluate the efficacy of this substance in reducing postoperative discomfort after oral surgical procedures(27).

Interpretation of Results

There were 4 randomized controlled trials included in this systematic review. According to (28), a total sample size of 84 was taken. Subjects were randomly allocated to 4 groups. Group A-control group, Group B- receiving oral bromelain 40mg, Group C- receiving 4mg submucosal dexamethasone and Group D- a combination of both C and D. Swelling was measured by means of 4 point method and mouth opening was measured by means of interincisal distance. Post operatively swelling and mouth opening was assessed on 2nd and 7th day. The results showed statistically significant difference in swelling among the combination group D when compared to individual group B and C. No significant differences in the amount of trismus were noted between the 4 groups at day 2 or 7.

According to (29), a total sample size of 100 was taken with patients having impacted mandibular third molar. Patients were divided randomly into two groups, irrespective of age and sex - each group consisting of 50 patients each. Group A receiving 4mg methylprednisolone and Group B receiving 10 mg serratiopeptidase. Post - operatively swelling and mouth opening was assessed on 1st, 3rd and 5th day. The results were statistically insignificant between group I and group II on the day 1 and 3. However, statistical significance was observed on day 5. Thus, serratiopeptidase has better efficacy in controlling postoperative

edema than methylprednisolone according to this study. Statistical significance was observed between group I and II ($P < 0.001$) resolution of trismus was better in group II than in group I. This attests to the probable fact that serratiopeptidase is better than methylprednisolone in resolving trismus post-operatively.

According (30), a total sample size of 110 was taken with Group 1 receiving 1 mg dexamethasone consisting of 40 participants and the Group 2 receiving 10mg serratiopeptidase consisting of 40 participants. Post – operatively swelling and mouth opening was assessed on 1st, 3rd, 5th and 7th day. There was statistically significant difference in pain, swelling and mouth opening between the groups in favour of drain group. Results showed, in the serratiopeptidase group, the swelling was highly significant on day 5, but reduced suddenly to insignificant swelling on day 7. This suggests that dexamethasone has better anti-inflammatory effect than serratiopeptidase. Both the dexamethasone and the serratiopeptidase groups showed statistically significant restricted mouth opening ($P < 0.012$ and $P < 0.019$, respectively) on day 5 and insignificant restricted mouth opening ($P < 0.114$ and $P < 0.223$, respectively) on day 7, suggesting that both the drugs were equally ineffective in relieving trismus.

According to (31), a total sample size of 150 was taken, which was further subdivided into 4 groups having 30 patients each. Only 2 groups relevant to this study were included, Group 1 receiving betamethasone 0.5mg and Group 2 receiving 20 mg serratiopeptidase each. Post operative swelling was measured on 1st, 3rd, 5th and 7th day. Mouth opening ability was assessed on 3rd and 5th day. In the betamethasone group, swelling was significantly greater ($p < 0.001$) compared with baseline until day 3. Betamethasone ($p < 0.01$) significantly improved mouth opening ability on day 3, and showed further improvement on day 5. Betamethasone was significantly superior to serratiopeptidase ($p < 0.001$).

Implications for Research

The number of good quality randomized controlled trials included in this review is very limited. There is a lack of evidence supporting the findings. Hence more long term randomized controlled trials are required to prove oral proteolytic enzymes help in reducing post-operative discomforts in mandibular third molar surgery. Our institution is passionate about high quality evidence based research and has excelled in various fields (32–42)

Conclusion

The number of good quality randomized controlled trials included in this review is very limited, from the above results we can conclude that corticosteroids are more effective in reducing swelling post third molar surgery. More properly designed randomized clinical trials are needed to evaluate the effectiveness of oral proteolytic enzymes in reducing post operative swelling following third molar surgery.

Summary

The aim of this systematic review is to evaluate the effectiveness of oral proteolytic enzymes versus corticosteroids in preventing post-operative complications in mandibular third molar surgery. There were 4 randomized controlled trials included in this systematic review. Among four clinical trials three clinical trials compared serratiopeptidase with dexamethasone and methylprednisolone. One clinical trial compared bromelain to dexamethasone. Risk of bias of included two trials are high, one trial is moderate and one trial is low. Hence the interpretations are less reliable. From this review, it can be concluded that corticosteroids are more effective in reducing swelling post third molar surgery.

Conflicts of interests

The author declares no conflicts of interest.

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