Role of Serratiopeptidase After Surgical Removal of Impacted Molar: A Systematic Review and Meta-analysis

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Abstract

Background Serratiopeptidase for pain, facial swelling and trismus associated with surgical removal of impacted molar is under investigation. However conclusive evidence on the use of serratiopeptidase is lacking. Hence a systematic review and meta-analysis of randomized controlled studies was carried out.

Methods Electronic databases were searched for eligible studies and necessary data extracted. The data were analysed using non-Cochrane mode in RevMan 5.0. 95% confidence interval (95% CI) was used to represent the deviation from the point estimate. The heterogeneity between the studies was assessed using Forest plot visually, I^2 statistics and Chi square test with a statistical P value of <0.10 to indicate statistical significance. Random-effect models were used in case of moderate to severe heterogeneity.

Results Five studies were included for final review. Serratiopeptidase improved trismus better than corticosteroids with the MD, 95% as 4.42 [3.84, 5]. As regards to swelling, no significant difference was observed for serratiopeptidase when compared to corticosteroids. Paucity of studies precludes any conclusion for other outcome measures as well as for other comparator drugs.

Conclusion Serratiopeptidase could be used safely and effectively to improve trismus and facial swelling after surgical removal of impacted molar.

Keywords Serratiopeptidase · Impacted molar · Serrapeptase

Introduction

Serratiopeptidase also known as serralysin, serrapeptase, serratiaptase, serratia peptidase, serratio peptidase, or serrapeptidase is a protease produced by *Enterobacterium serratia*. It is widely used in medical field as an anti-inflammatory [1] and analgesic [2]. Reports also suggest anti-sclerotic, fibrinolytic and caseinolytic properties of serratiopeptidase.² In the field of dentistry, serratiopeptidase is being considered for post-operative reduction of pain and swelling after minor surgical procedures [3–5]. An audit on prescription patterns of dentists in a tertiary care hospital, identified the use of serratiopeptidase by majority of dentists without adequate justification [6]. The most common minor surgical procedure in a dental set up is removal of impacted molar teeth and the related post-operative effects include pain, trismus and facial swelling [7–9]. Serratiopeptidase has been suggested by various authors for its analgesic and anti-inflammatory effects after impacted third molar removal [10, 11]. A systematic review on serratiopeptidase by Bhagat et al. [12] compiled the findings of various randomized controlled trials on serratiopeptidase in both medical and dental practice. However as regards to dentistry, the indication was not addressed in detail and meta-analytic principles were not applied. Hence this systematic review and meta-analysis will aim to identify and confirm the anti-inflammatory and analgesic

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effects of serratiopeptidase in reducing pain, trismus and facial swelling compared to any other drug, after surgical removal of impacted molar.

Methods

Information Sources and Search Strategy

The protocol for this review was registered with International prospective register of systematic reviews (PROSPERO) with the registration number CRD42016033102. The review protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016033102. A thorough literature search was conducted and was completed on 13 January 2016. The primary data base used was Medline (via PubMed), Cochrane central register of clinical trials (CENTRAL) and Database of Abstracts of Reviews of Effects (DARE). The key words used were serratiopeptidase [tiab] AND impacted [tiab]. This search was further supplemented by hand searching of relevant references from review articles and other eligible studies. No limits were applied to the year of study, but only studies published in English language were included.

Eligibility Criteria

Only those studies with randomized controlled design with the following requirements were included in the present study:

1. *Type of participants* Patients who underwent surgical removal of impacted molar tooth
2. *Type of intervention* Serratiopeptidase alone or in combination with any other drug, irrespective of dose and duration
3. *Comparison* Any other drug or placebo
4. *Outcome* Pain, facial swelling and restricted mouth opening (trismus) associated with surgical removal of impacted molar teeth.

Study Procedure

Both the authors independently screened the data bases and independently reviewed the identified abstracts for suitability. Full-texts articles were obtained following abstract screening for those found to be eligible to be included in the review. A pre-tested data extraction form was created and both the authors independently extracted the following data from each eligible study: trial site, year, trial methods, participants, interventions, and outcomes. Disagreement between the authors was resolved through discussion. The extracted data were analysed

using non-Cochrane mode in RevMan 5.3 software. The methodological quality of eligible trials was independently assessed by both the authors using The Cochrane collaboration's tool for assessing the risk of bias. We followed the guidance to assess whether trials took adequate steps to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. The judgement was categorized into low, high or unclear risk of bias [13]. Mean difference (MD) between the serratiopeptidase (experimental) and other drugs such as corticosteroids, paracetamol, ibuprofen and bromelain (control) were assessed from each of the eligible studies and the mean difference and standard error were considered for final assessment of the efficacy. 95% confidence interval (95% CI) was used to represent the deviation from the point estimate. The heterogeneity between the studies were assessed using Forest plot visually, I^2 statistics wherein more than 50% was considered to have moderate to severe heterogeneity and Chi square test with a statistical P value of <0.10 to indicate statistical significance. Random-effect models were used in case of moderate to severe heterogeneity (I^2 values more than 75%). Considering the presence only five eligible trials, publication bias could not be assessed. The present meta-analysis was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The grading of quality of included studies was carried out as per Cochrane's grading of recommendations assessment, development and evaluation tool (GRADE) [15].

Results

Search Results

A total of three studies were screened from Cochrane, PubMed and DARE and removing the duplicates. Two more studies were obtained on reference screening of the included studies. Altogether 5 studies [16–20] were included in the present review. Figure 1 depicts the study flow chart. Publication bias could not be checked as there were only five eligible studies for inclusion in this review. The risk of bias table is depicted in Table 2 [16–20]. Table 1 shows the list of included studies with the key study details [16–20]. Studies compared the efficacies of serratiopeptidase with bromelain [20], paracetamol [17], methylprednisolone [19] and dexamethasone [18]. Chopra et al. [16] compared the efficacy of serratiopeptidase with paracetamol, ibuprofen and betamethasone. One of the included

Fig. 1 Study flow chart

studies [16] was high quality and all others were moderate quality as per GRADE (Table 2).

Pooled Results

Pain

All except one study¹⁹ mentioned numerical values for pain and were included in the pooled analysis. Since one each of the studies compared the effect of serratiopeptidase with other agents, pooling the results was not possible and meta-analysis could not be attempted for this outcome measure.

Facial Swelling

Two of the included studies compared facial swellings between serratiopeptidase and corticosteroids and the pooled analysis is depicted in Fig. 2. Corticosteroids reduced swelling better than serratiopeptidase {MD, 95% CI 2.95 [0.83, 5.07]}. Further, sub-group analyses revealed

significant decrease in the swelling only on day 1 but not thereafter. Only one study each was obtained comparing serratiopeptidase with other drugs and so pooling of the results was not possible.

Trismus

Serratiopeptidase was found to improve trismus better than corticosteroids (Fig. 3) with the MD, 95% as 4.42 [3.84, 5]. Further, sub-group analyses revealed a significant reduction with serratiopeptidase on day 1, 3, 5 and 7. Only one each study was obtained comparing serratiopeptidase with other drugs and so pooling of the results was not possible.

Grade

Grading of the quality of evidence was done by GRADE approach for facial swelling and trismus and low quality was obtained due to serious imprecision and risk of bias (Table 3).

Discussion

The present systematic review is an attempt to compile the available evidences on the use of serratiopeptidase in reducing pain, facial swelling and trismus after surgical removal of impacted molar tooth. A total of 5 studies were found eligible to be included. A statistically significant improvement in trismus has been demonstrated in comparison with corticosteroids and ibuprofen. Although on the immediate post-operative day, corticosteroids were found to outperform serratiopeptidase in reducing the facial swelling, no significant difference was observed thereafter. Pooling of the results could not be performed for pain because of the paucity of eligible studies.

Serratiopeptidase is a proteolytic enzyme which is being used alone or in combination with steroids and NSAID's for effective relief from pain and swelling [2]. It is usually administered orally, absorbed through the intestine and directly transported into the bloodstream. However due to its peptide nature, there is greater tendency to undergo enzymatic degradation in the gastrointestinal tract, leading to poor bioavailability [21]. Enteric coated formulations are available in the market to overcome poor bio availability. In dental practice minor surgical procedures often are associated with post-operative pain and swelling which is annoying to the patient. In particular, it is more often a source of great discomfort after surgical removal of an impacted molar tooth. Serratiopeptidase is being used by dentists to combat post-operative pain, swelling and trismus associated with surgical removal of impacted molar. The anti-inflammatory activity is attributed to increase in

Table 1 List of included studies

References	Participants	Intervention	Control	Outcome
Chopra et al. [16]	150 patients with impacted lower third molar requiring surgical removal within the age group of 18–45 years	Serratiopeptidase 20 mg 3 times in a day for 7 days	Ibuprofen 600 mg with betamethasone 0.5 mg and paracetamol 1000 mg or placebo	Swelling measured at 0, 1, 3, 5 and 7 days Pain measured at 0, 30 min and after 1 h and 1–7 post-operative days Mouth opening measured at days 3 and 5 post-operatively
Al-Khateeb et al. [17]	24 patients with impacted molar teeth requiring surgical removal within the age group of 20–27 years	Serratiopeptidase 5 mg with 1000 mg paracetamol every 8 hourly for 7 days	1000 mg paracetamol with placebo	Swelling, pain and mouth opening ability measured at 1st, 2nd, 3rd and 7th post-operative days
Murugesan et al. [18]	110 patients with impacted mandibular molar requiring surgical removal	Serratiopeptidase 10 mg three times a day for 3 days	1 mg dexamethasone three times daily for 3 days	Swelling, pain and mouth opening ability measured at 1, 3, 5 and 7th post-operative days
Chappi et al. [19]	100 patients with impacted molar requiring surgical removal	Serratiopeptidase 10 mg oral twice a day for 5 days	Methylprednisolone 4 mg oral 8 hourly for 5 days	Facial swelling, pain and mouth opening measured at 0, 1, 3 and 5th day
Kannan et al. [20]	90 patients within age group of 20–35 years with impacted molar tooth requiring surgical removal	Amoxicillin 500 mg + Metronidazole 200 mg + Diclofenac 20 mg + Serratiopeptidase 10 mg twice daily for 5 days	Amoxicillin 500 mg + Metronidazole 200 mg + Diclofenac 20 mg twice daily for 5 days Or Amoxicillin 500 mg + Metronidazole 200 mg + Diclofenac 20 mg + Bromelain 200 mg twice daily for 5 days	Pain, facial swelling and mouth opening measured at 0, 1, 2 and 7 days

Table 2 Risk of bias as per ‘The Cochrane Collaboration’s tool for assessing the risk of bias’

Study ID	Al-Khateeb and Husair [17]	Chopra et al. [16]	Murugesan et al. [18]	Chappi et al. [19]	Kannan et al. [20]
Sequence generation	High	Low (computer generated)	High	High	High
Allocation concealment	High	High	High	High	High
Blinding	Unclear	Low (double blinded)	High	High	High
Selective reporting	Low	Low	Low	Low	Low
Incomplete outcome	Low	Low	Low	Low	Low

the viscosity of accumulated fluid facilitating drainage. It can modify cell-surface adhesion molecules that attract inflammatory cells to their target site [22]. The analgesic activity is related to the inhibition of pain inducing bradykinin and other amines [1]. As regards to the safety of use, there has not been any published reports on adverse drug reactions to serratiopeptidase. However possible reactions include skin reactions, muscle and joint pain, anorexia, nausea, cough and coagulation disturbances [23]. The dosage recommended in various studies ranged

between 10 and 60 mg per day, however dosage for specific indications had not been addressed till date [3]. This brings in the need to set guidelines on the dose and regimen, which is indication specific. There has been no published data regarding drug interactions with Serratiopeptidase; however administration with warfarin, aspirin or clopidogrel has been suggested to increase the risk of bleeding or bruising [12]. Although Mazzone et al. [24] in a multicentric, double blinded randomized controlled study established a significant anti-inflammatory, anti-oedematic

Fig. 2 Forest plot comparing the facial swelling for serratiopeptidase group with corticosteroids

Fig. 3 Forest plot comparing the mouth opening ability of serratiopeptidase group with corticosteroids

and fibrinolytic activity of Serratiopeptidase in acute or chronic ear, nose or throat disorders in comparison to placebo, we did not identify significant analgesic activity of serratiopeptidase after impacted molar surgery. We hypothesize this discrepancy to the more severe inflammation seen after impacted molar tooth surgery than the

non-surgical inflammation. Also the present review compared the effect of serratiopeptidase with other active drugs like paracetamol, ibuprofen, corticosteroids and bromelain while in the earlier study [24] it was placebo. Erythema, dermatosis and minor coagulation problems have been reported with Serratiopeptidase to a minor extent [12].

Table 3 Grading the evidence using GRADE approach

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Absolute	
Facial swelling (better indicated by lower values)								
2	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^b	None	MD 1.34 higher (0.89–1.79 higher)	⊕⊕ Low
Mouth opening ability (better indicated by lower values)								
2	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^b	None	MD 5.76 higher (3.62–7.9 higher)	⊕⊕ Low

^a Both the studies have not disclosed the method of randomization, allocation concealment and more importantly, open labeled

^b Small sample size

MD mean difference

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate

The present review is limited in the following aspects: although a vast majority of the databases were searched for the availability of literature, we did not include EMBASE due to constraints in the access and therefore led to limited number of study participants in the pooled analysis. Despite this minor limitation, we conclude from the present review that serratiopeptidase improves trismus significantly greater than corticosteroids but a similar effect could be observed for facial swelling as well. As it has better safety profile than the other counterparts such as non-steroidal anti-inflammatory agents and corticosteroids, serratiopeptidase can be considered as an alternative drug in case of intolerance or contra-indication to other drugs.

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Compliance with Ethical Standards

Conflict of interest None of the authors have any conflict of interest.

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