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REVIEW

EFFICACY OF SERRATIOPEPTIDASE IN THIRD MOLAR SURGERY. A SYSTEMATIC REVIEW AND META-ANALYSIS

Eficacia de la serratiopeptidasa en cirugía del tercer molar. Una revisión sistemática y un metanálisis

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ABSTRACT

Objective: To determine the efficacy of serratiopeptidase in third molar surgery.

Materials and Methods: A bibliographic search was carried out until April 2022, in the biomedical databases: *Pubmed/Medline, Cochrane Central Registry of Clinical Trials, Scopus, Scielo* and *Google Scholar.* Studies reporting the efficacy of serratiopeptidase in third molar surgery, which were randomized clinical trials, in English and without time limits, were included. The RoB 2.0 tool was used to assess the risk of the included studies and the GRADEPro GDT tool to assess

Results: The preliminary search yielded a total of 116 articles, discarding those that did not meet the selection criteria, leaving only 10 articles. Six articles entered a meta-analysis and found that serratiopeptidase reduces trismus but not reduce inflammation and pain after third molar surgery.

Conclusions: The literature reviewed suggests that serratiopeptidase is effective in reducing trismus after third molar surgery.

Keywords: *Serratiopeptidase; Molar, Third; Inflammation; Pain; Trismus; Meta-Analysis.*

RESUMEN

Objetivo: Determinar la eficacia de la serratiopeptidasa en la cirugía del tercer molar.

Materiales y Métodos: Se realizó una búsqueda bibliográfica hasta abril de 2022, en las bases de datos biomédicas: *Pubmed/Medline, Registro Cochrane Central de Ensayos Clínicos, Scopus, Scielo* y *Google Scholar.* Se incluyeron estudios que reportaron la eficacia de la serratiopeptidasa en cirugía de terceros molares, que fueron ensayos clínicos aleatorios, en inglés y sin límite de tiempo. Se utilizó la herramienta RoB 2.0 para evaluar el riesgo de los estudios incluidos y la herramienta GRADEPro GDT para evaluar la calidad de la evidencia y la fuerza de recomendación de los resultados.

Resultados: La búsqueda preliminar arrojó un total de 116 artículos, descartando aquellos que no cumplieron con los criterios de selección, quedando solo 10 artículos. Seis artículos participaron en un metanálisis y encontraron que la serratiopeptidasa reduce el trismo, pero no reduce la inflamación y el dolor después de la cirugía del tercer molar.

Conclusión: La literatura revisada sugiere que la serratiopeptidasa es efectiva para reducir el trismo después de la cirugía del tercer molar.

Palabras Clave: *Serratiopeptidasa; Tercer molar; Inflamación; Dolor; Trismo; Metaanálisis.*

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INTRODUCTION

Third molar extraction is one of the most common procedures performed by oral and maxillofacial surgeons. After extraction of impacted third molars in the early postoperative period, patients often present complications such as pain, swelling, and lockjaw.[1,2]

Appropriate surgical methods, such as selection of an appropriate flap design, minimal bone removal, and less trauma to adjacent soft tissues with proper wound closure techniques, may decrease the incidence of postoperative sequelae, but not eliminate them.[3] These complications are resolved in two weeks, the time needed to recover their quality of life.[4]

Over the years, alternative therapies such as laser and piezoelectric instruments have been sought to reduce the postoperative sequelae of third molar surgery.[5,6]

Mouth rinses, antibiotics, analgesics, topical gels, cryotherapy, ozone therapy, platelet-rich fibrin, kinesiotaping, and corticosteroids have also been used to reduce pain, inflammation, and trismus after third molar surgeries.[7-10]

In addition, the pharmaceutical industry has contributed various drugs, such as corti-costeroids and non-steroidal anti-inflamma-tory drugs (NSAIDs), to suppress inflamma-tion. However, the use of these drugs has been associated with some adverse effects, such as gastrointestinal bleeding, impaired renal function, reduced platelet function, difficulty breathing and profound hypotension.[11] Alternative NSAIDs formulations such as celecoxib have shown less gastrointestinal toxicity.[12]

Recently, enzyme-based therapy is gaining more attention due to its selectivity, efficiency, and safety profile.[13]

Serratiopeptidase, also known as serralysin, serrapeptase, serratiapeptase, serratia-peptidase, serratio peptidase or serrapeptidase, is an extracellular metallo-protease produced by the *bacterium Serratia sp.*, widely used in therapeutic applications.

It has shown significant anti-inflammatory and analgesic effects in various areas of surgery, orthopedics, otorhinolaryngology, gynecology and dentistry.[14] Its anti-inflammatory action is attributed to the fact that it reduces inflammatory cytokines and adhesion molecules, thus regulating the movement of inflammatory cells to-wards the site of inflammation.[13,15]

The analgesic activity is related to its ability to hydrolyze bradykinin, histamine and serotonin.[14] It is normally recommended to take it orally at a dose of 5 mg to 10 mg three times a day, it is absorbed through the intestine and transported directly into the bloodstream. However, due to its peptide nature, there is a greater tendency to undergo enzymatic degradation in the gastrointestinal tract, leading to low bioavailability.

For this reason, the new pharmacological formulations of this drug have an enteric coating to overcome this low bioavailability.[16]

Regarding the safety of use, no report on the appearance of adverse reactions to serratiopeptidase has been published.[17]

However, possible reactions include skin reactions, muscle and joint pain, anorexia, nausea, cough and coagulation disorders.[14]

Two systematic reviews on the use of serratiopeptidase, conducted by Bhagat *et al.*,[18] and Sivaramakrishnan *et al.*,[19] compiled the results

of several randomized controlled clinical trials (RCTs) on the use of serratiopeptidase in medical and dental practice.

However, the pharmacological actions of serratiopeptidase are debated and so far there is no conclusive statement on its efficacy, despite the fact that more clinical studies on its efficacy in dental practice have been conducted in recent years. Therefore, the objective of this study is to determine the efficacy of serratiopeptidase in third molar surgery.

MATERIALS AND METHODS

Protocol and registration

The protocol for this systematic review was defined *a priori* by all authors and was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[20] In addition, this protocol was registered in the Prospective International Register of Systematic Reviews (PROSPERO) with the registration number CRD42022333514.

To prepare and structure this review, the focused question was formulated using the PICO format (population, intervention, outcomes and results) as detailed below:

- Population: Patients who received an extraction of third molars.
- Intervention: Patients who received serratiopeptidase.
- Comparison: Patients who received a drug other than serratiopeptidase or who received a placebo.
- Outcomes: Reduction of trismus, pain and inflammation.

Focused question (PICO)

Is serratiopeptidase effective in third molar surgery?

Search and selection of studies

For the present systematic review, a bibliographic search was carried out in 5 electronic databases (*Pubmed/Medline, Cochrane Central Registry of Clinical Trials, Scopus, Scielo and Google Scholar*) until April 2022; combining keywords and subject titles according to the thesaurus of each database: "*serratiopeptidase*", "*serrapeptase*", "*third molar surgery*", "*third molar*" and "*dental extraction*". The search strategies of each of the databases are found in Table 1.

Additionally, additional relevant literature was included after a hand search of the reference lists of the final included articles.

The search in the electronic database was carried out by two authors (HA and AR) independently, and the final inclusion decision was made according to the following criteria: RCTs in English, without time limit and reporting efficacy of serratiopeptidase in third molar surgery. Articles that were prospective studies and unpublished studies were excluded.

Data extraction

A predefined table was used to extract data from each eligible study, including: author(s), year of publication, type of RCT, total number of patients, total proportion of men and women, mean age, age range, time of follow-up, study groups, initial and final number of patients per study group, country where the study was conducted, reduction of trismus, pain and inflammation, and conclusions.

From each eligible study, two investigators (TC and FC) independently extracted information

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and all disagreements were resolved by discussion with a third reviewer (AV).

Risk of bias (RoB) assessment

The RoB of the included studies was independently assessed by two calibrated authors (TC and FC) (k = 0.98) using the RoB 2.0 tool[21] and all disagreements were resolved by discussion with a third reviewer (AV).

According to this tool, randomized clinical trials are evaluated in 5 domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result; to later be classified as risk: low, with some concerns and high.

Analysis of results

Data from each study were entered and analyzed in RevMan 5.3 (Cochrane Group, UK); using the mean difference as a measure, in a random effects model with a 95% confidence

Figure 1. PRISMA flow chart of the process of inclusion and exclusion of studies in the systematic review.

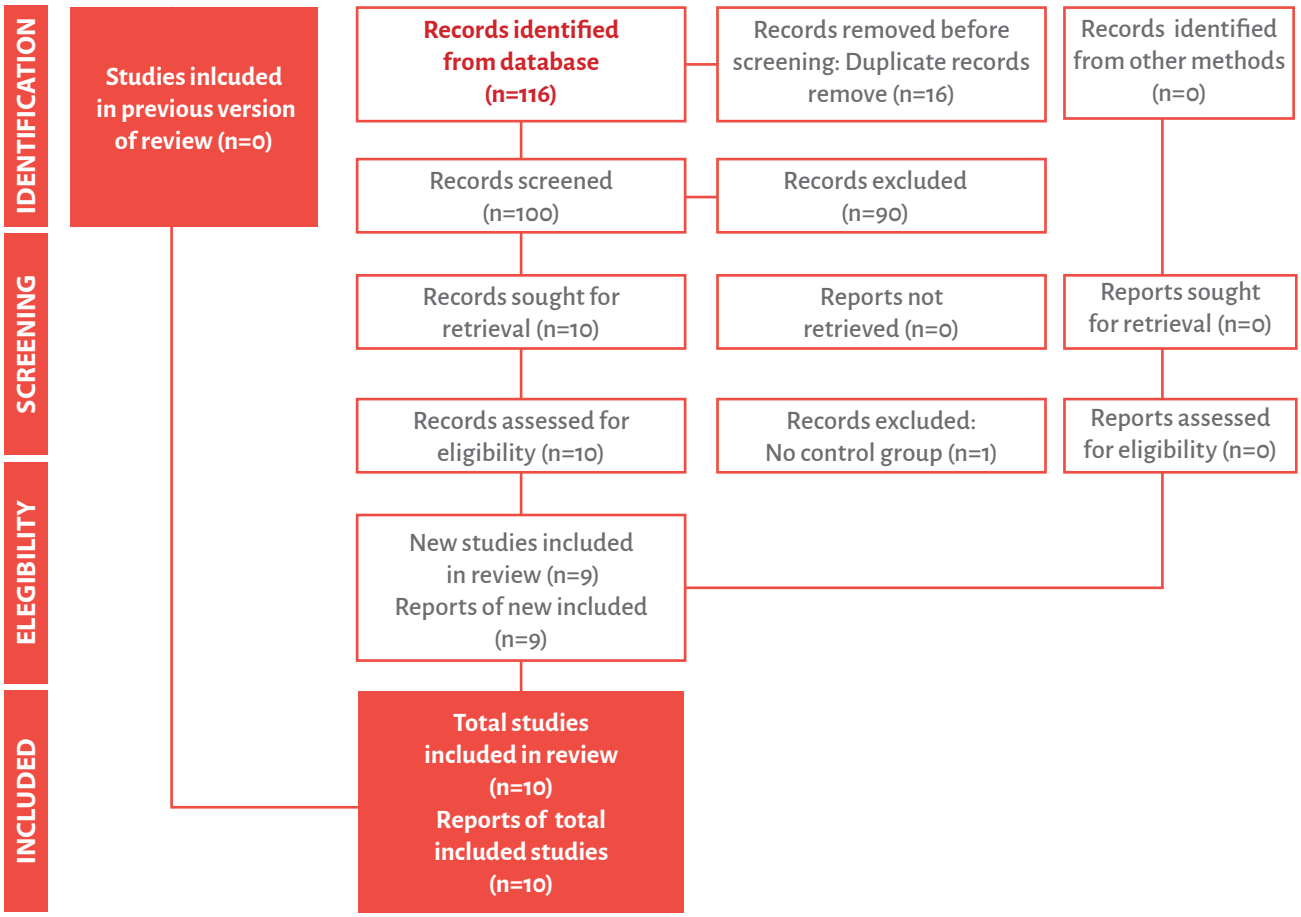
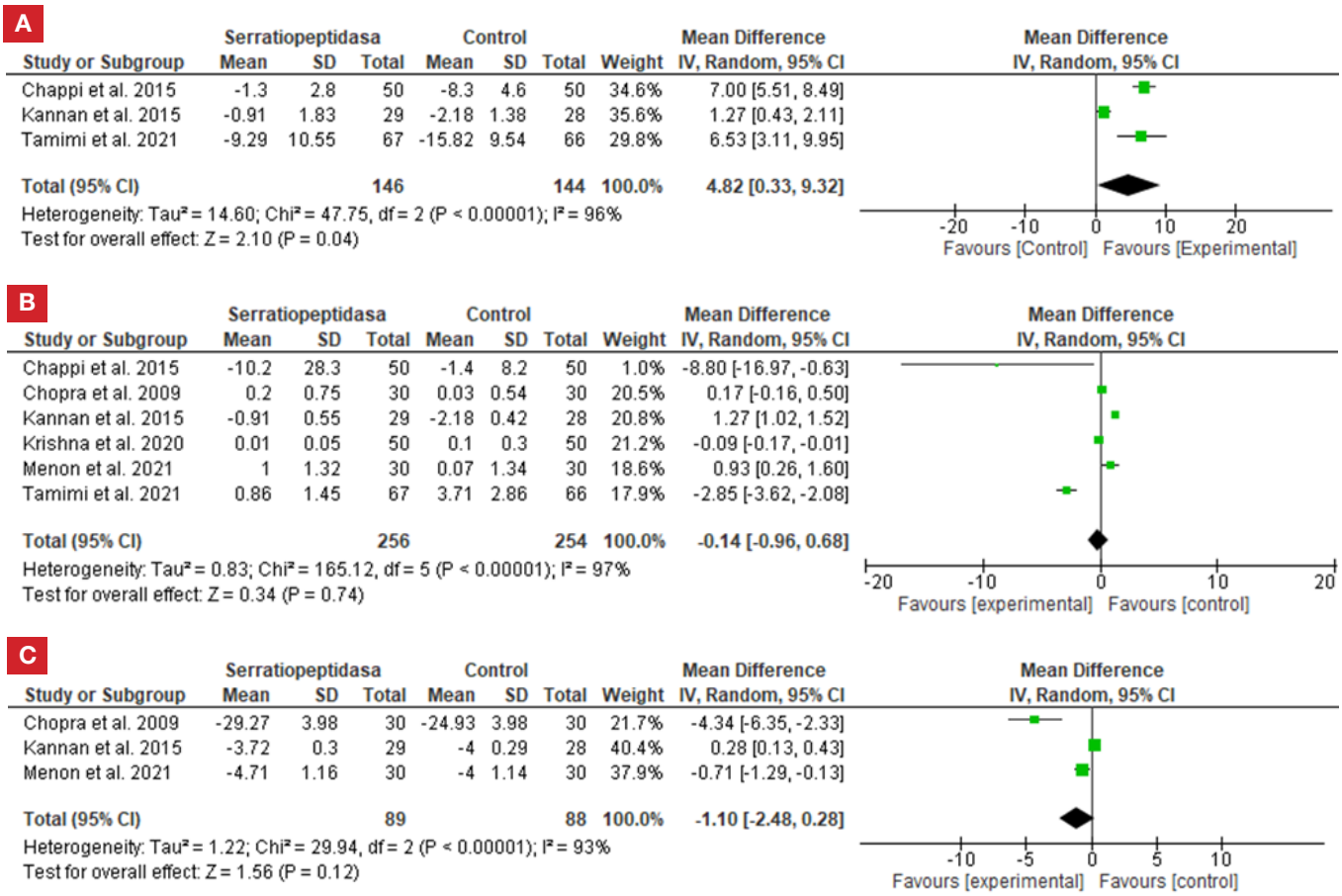


Figure 2. Risk of bias of included studies.

Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
Tamimi et al.	Serratiopeptidase + Paracetamol	Paracetamol + Placebo	+	+	+	+	+	+
Menon et al.	Diclofenac + serratiopeptidase	Bromelain + trypsin + rutoside	+	+	+	+	+	+
Ramasubbu et al.	Amoxicillin + metronidazole + diclofenac + serratiopeptidase	Amoxicillin + metronidazole + diclofenac + bromelain	+	+	+	+	+	+
Al-Moraissi et al.	Serratiopeptidase	Submucosal chymotrypsin or Dexamethasone	+	+	+	+	+	+
Krishna et al.	Serratiopeptidase	Dexamethasone	+	+	+	-	+	-
Chappi et al.	Serratiopeptidase	Methylprenidsolone	+	+	+	-	+	-
Murugesan et al.	Serratiopeptidase	Dexamethasone	+	+	+	-	+	-
Chopra et al.	Serratiopeptidase	Ibuprofen or Betamethasone or Paracetamol or Placebo	+	+	+	+	+	+
Al-Khateeb et al.	Serratiopeptidase	Paracetamol	+	+	+	-	+	-

Figure 3. Meta-analysis of the efficacy of serratiopeptidase in reducing trismus, inflammation and pain.



A. Trismus. **B.** Inflammation. **C.** Pain.

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Table 1. Search strategies for each database.

DATABASE	SEARCH STRATEGY
Pubmed/Medline	((*serratiopeptidase*) OR serrapeptase) AND (((*"third molar surgery"*) OR *"Third molar"*) OR *"dental extraction"*) Cochrane *Central* Registry of Clinical Trials #1 (*"serratiopeptidase"*) OR OR (*"serrapeptase"*) (*Word variations have been searched*) #2 MeSH descriptor: [*Molar, third*] explode all trees #3 (*"third molar surgery"*) OR (*"third molar"*) OR (*"dental extraction"*) (*Word variations have been searched*) #4 #2 OR #3 #5 #1 AND #4
Scopus	(TITLE-ABS-KEY (*serratiopeptidase*) OR TITLE-ABS-KEY (*serrapeptase*)) AND (TITLE-ABS-KEY (*"third molar surgery"*) OR TITLE-ABS-KEY ("third molar") OR TITLE-ABS-KEY (*"dental extraction"*)) AND (TITLE-ABS-KEY (clinical AND trial)) AND (LIMIT-TO (DOCTYPE, *"ar"*)) AND (LIMIT-TO (SUBJAREA, *"DENT"*)) AND (LIMIT-TO (SRCTYPE, *"j"*))
Scielo	((serratiopeptidase) OR (serrapeptase)) AND ((*"third molar surgery"*) OR (*"third molar"*) OR (*"dental extraction"*))
Google Scholar	*"serratiopeptidase"* OR *"serrapeptase"* + *"third molar surgery"* OR *"third molar"* OR *"dental extraction"* + *"clinical trial"* -*"in vitro"*

Table 2. Reason for exclusion of the studies.

AUTHORS	EXCLUSION REASON
Tharani Kumar *et al.*[22]	It does not have a control group

interval. Additionally, a GRADE analysis was performed using the guideline development tool (GRADEPro GDT) (McMaster University and Evidence Prime Inc., Canada).

RESULTS

Selection of studies

The electronic and manual search strategy yielded a total of 116 articles, excluding 16 duplicates (Figure 1). After title and abstract screening, 10 potentially eligible full-text articles were selected.

As a result, 1 study was excluded,[22] resulting in 9 RCTs that met the eligibility criteria and 1 RCT obtained from a previous systematic review was added, making a total of 10 RCTs for qualitative synthesis and 6 RCTs for quantitative synthesis. The reasons for exclusion of the studies are found in Table 2.

Characteristics of included studies

Overall, 10 RCTs[3,11,23–30] were included, of which only 1 was crossover.[30] The years of publication, the total number of patients, the mean age, the age range and the follow-up time ranged between 2008 and 2021, 24 and 150 patients, 22.5 and 29.5 years, 18 and 45 years and from 5 to 7 days, respectively. The countries where the studies were carried out were: Jordan,[11,30] India,[23–29] and Yemen,[3] (Table 3).

Table 3. Characteristic of included studies.

Author Year Country	Type of study	Number of patients (M/F)	Mean age (range)	Follow-up time	Study groups	Number of patients per group	Final number of patients per group	Trismus Initial	Trismus Final	Trismus Reduction	Pain Initial	Pain Final	Pain Reduction
Tamimi et al. (11) 2021 Jordan	Double blind parallel RCT	140 (64/76)	22.9 (19 - 41)	5 days	Serratiopeptidase 10mg + Paracetamol 1g	70	67	45.84 ± 7.1	36.55 ± 7.8	- 9.29 ± 10.55	NR	NR	NR
					Paracetamol 1g + Placebo	70	66	44.84 ± 5.9	29.02±7.5	- 15.82 ± 9.54	NR	NR	NR
Menon et al. (23) 2021 India	Double blind parallel RCT	60 (33/27)	29.5 (18 - 40)	7 days	Bromelain 90mg + trypsin 48mg + rutoside 100mg	30	30	NR	NR	NR	5 ± 0.71	1 ± 0.89	- 4 ± 1.14
					Diclofenac 50mg + serratiopeptidase 10mg	30	30	NR	NR	NR	5.5 ± 0.84	0.79 ± 0.8	- 4.71 ± 1.16
Ramasubbu et al. (24) 2021 India	Parallel RCT	60	(20 - 40)	7 days	Amoxicillin 500mg + metronidazole 200mg + diclofenac 50mg + bromelain 200mg	30	30	41.07	43.43	2.4	3.267	1.267	- 2
					Amoxicillin 500mg + metronidazole 200mg + diclofenac 50mg + serratiopeptidase 10mg	30	30	38.37	41.63	3.26	5.4	4.333	- 1.07
Al-Moraissi et al. (3) 2020 Yemen	Double blind parallel RCT	60 (25/35)	29.13 ± 8 (19 - 39)	5 days	Submucosal chymotrypsin 5mg	20	20	4.06 ± 0.68	NR	NR	1 (0 - 3)	NR	NR
					Serratiopeptidase 5mg	20	20	4.16 ± 0.78	NR	NR	0 (0 - 2)	NR	NR
					Dexamethasone 8mg	20	20	3.81 ± 0.66	NR	NR	1 (0 - 2)	NR	NR
Krishna et al. (25) 2020 India	Parallel RCT	100 (63/37)	26.5	7 days	Serratiopeptidase 10mg	50	50	NR	NR	NR	NR	NR	NR
					Dexamethasone 1mg	50	50	NR	NR	NR	NR	NR	NR
Chappi et al. (26) 2015 India	Parallel RCT	100	NR	5 days	Methylprednisolone 4mg	50	50	NR	NR	- 8.3 ± 4.6	NR	NR	- 8.3
					Serratiopeptidase 10mg	50	50	NR	NR	- 1.3 ± 2.8	NR	NR	- 1.3

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Author Year Country	Type of study	Number of patients (M/F)	Mean age (range)	Follow-up time	Study groups	Number of patients per group	Final number of patients	Results					
								Trismus				Pain	
								Initial	Final	Reduction	Initial	Final	Reduction
Kannan et al. (27) 2015 India	Parallel RCT	90	28.13 ± 1.07 (20 – 35)	7 days	Amoxicillin 500 mg + metronidazole 200 mg + Diclofenac 50 mg	30	28	29.89 ± 0.34	27.71 ± 1.34	- 2.18 ± 1.38	4.96 ± 0.22	0.96 ± 0.19	- 4 ± 0.29
					Amoxicillin 500 mg + metronidazole 200 mg + diclofenac 50 mg + bromelain 200 mg	30	28	28.44 ± 0.82	27.51 ± 0.9	- 0.93 ± 1.22	3.96 ± 0.19	0.79 ± 0.13	- 3.17 ± 0.23
					Amoxicillin 500 mg + metronidazole 200 mg + diclofenac 50 mg + serratiopeptidase 10 mg	30	29	28.52 ± 0.83	27.61 ± 1.63	- 0.91 ± 1.83	4.55 ± 0.23	0.83 ± 0.19	- 3.72 ± 0.3
Murugesan et al. (28) 2012 India	Parallel RCT	110	NR	7 days	Dexamethasone 1mg	55	55	4.7 ± 1.0	4.8 ± 1.06	0.69 ± 0.18	NR	NR	NR
					Serratiopeptidase 10mg	55	55						
Chopra et al. (29) 2009 India	Double blind parallel RCT	150 (92/58)	28.05 (18 - 45)	7 days	Ibuprofen 600mg	30	30	NR	NR	NR	24.2 ± 3.09	0.00	- 24.2 ± 3.09
					Betamethasone 0.5mg	30	30	NR	NR	NR	28.37 ± 3.33	0.00	- 28.37 ± 3.33
					Paracetamol 1g	30	30	NR	NR	NR	29.27 ± 3.98	0.00	- 29.27 ± 3.98
					Serratiopeptidase 20mg	30	30	NR	NR	NR	25.6 ± 3.39	0.67 ± 0.46	- 24.93 ± 3.42
					Placebo	30	30	NR	NR	NR	37.07 ± 3.12	5.0 ± 1.91	- 32.07 ± 3.66
Al-Khateeb et al. (30) 2008 Jordan	Double blind parallel RCT	24 (10/14)	22.5 ± 1.7 (20 - 27)	7 days	Serratiopeptidase 5mg	24	24	0.0125 ± 0.65893	0.175 ± 0.65955	0.16 ± 0.66	2.625 ± 1.68916	0.375 ± 1.0135	- 2.25 ± 1.47

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Table 3. Characteristic of included studies.

Author	Results															
	Swelling or Inflammation															
	Tragus - Pogonion (DHS)			Tragus - Mouth (DHC)			Gonion - Canthus (DV)			Face measurement			Cheek circumference		
	Initial	Final	Reduction	Initial	Final	Reduction	Initial	Final	Reduction	Initial	Final	Reduction	Initial	Final	Reduction
Tamimi et al.[11]	147.14 ± 10.2 146.01 ± 13.6	148.1 ± 9.1 150.1 ± 14.1	0.96 ± 13.67 4.09 ± 19.59	108.41 ± 8.6 109.98 ± 9.7	109.29 ± 8.2 114.01 ± 9.8	0.86 ± 1.45 3.71 ± 2.86	104.26 ± 13.4 103.98 ± 9.9	104.73 ± 13.5 106.19 ± 9.7	0.45 ± 0.97 2.47 ± 2.37	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Menon et al.[23]	14.57 ± 0.94 14.57 ± 0.94	14.64 ± 0.95 15.57 ± 0.93	0.07 ± 1.34 1.00 ± 1.32	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR
Ramasubbu et al.[24]	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	26.93 27.5	20.97 25.23	- 5.96 - 2.27	NR NR	NR NR	NR NR
Al-Moraissi et al.[3]	12.405 (1.5) 12.215 (1.568) 11.895 (1.58)	NR NR NR	NR NR NR	11.51 (1.54) 10.77 (1.45) 10.525 (1.70)	NR NR NR	NR NR NR	11.315 (2.36) 9.44 (1.42) 9.63 (1.83)	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR
Krishna et al.[25]	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	475.6 ± 73.4 431.6 ± 83.7	476.3 ± 72.9 430.1 ± 84.4	0.7 ± 3.1 1.5 ± 14.3	29.8 ± 4.3 29.6 ± 4.9	29.7 ± 4.3 29.7 ± 4.9	0.01 ± 0.05 0.1 ± 0.3
Chappi et al.[26]	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	- 1.4 ± 8.2 - 10.2 ±28.3
Kannan et al.[27]	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR	29.89 ± 0.31 28.44 ± 0.33 28.52 ± 0.4	27.71 ± 0.28 27.51 ± 0.33 27.61 ± 0.38	- 2.18 ± 0.42 - 0.93 ± 0.47 - 0.91 ± 0.55
Murugesan 0.554 et al.[28]	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	12.036 ± 7.188	12.127 ± 7.177	0.091 ± 0.175	0.491 ± 1.219	1.364 ± 1.175	0.873 ±
Chopra et al.[29]	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	42.36 ±0.46 43.34 ± 0.38 43.30 ± 0.53 43.03 ± 0.36 43.3 ± 0.43	42.50 ± 0.46 43.37 ± 0.38 43.37 ± 0.53 43.23 ± 0.36 44.54 ± 0.42	0.14 ± 0.65 0.03 ± 0.54 0.07 ± 0.75 0.2 ±0.75 1.24 ± 0.6
Al-Khateeb et al.[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.1833 ± 0.46219	0.1542 ± 0.15598	- 0.03 ± 0.41

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Table 4. GRADE analysis

CERTAINTY ASSESSMENT							CERTAINTY
NUMBER OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDE-RATIONS	
3	*RCT*	*serious*	*very serious*	*not serious*	*not serious*	*none*	⊕◯◯◯ *Very low*
Efficacy in reducing inflammation (follow-up: range 5 days to 7 days)							
6	*RCT*	*serious*	*very serious*	*not serious*	*not serious*	*none*	⊕◯◯◯ *Very low*
Efficacy in reducing pain (follow-up: range 5 days to 7 days)							
3	*RCT*	*serious*	*very serious*	*not serious*	*not serious*	*none*	⊕◯◯◯ *Very low*

All studies reported a group of patients who received serratiopeptidase alone[3,25,26,28–30] or in combination with other drugs[11,23,24,27] and at least one control group who received other drugs or a drug with a placebo or only a placebo. Of all the studies, only 7, 10 and 7 studies reported data on trismus, inflammation and pain, respectively (Table 3).

Risk of bias analysis of studies

Five studies[3,11,23,24,27] were at low risk of bias and the remaining[25,26,28–30] were at high risk of bias (Figure 2).

Synthesis of the results (Meta-analysis)

The efficacy of serratiopeptidase in reducing trismus, inflammation and pain was determined in three,[11,26,27] six[11,23,25–27,29] and three[23,27,29] studies. Showing that there was a statistically significant difference in the reduction of trismus (p = 0.04, I_2 = 96%, MD = 4.82 [0.33 – 9.32]) and there was no statistically significant difference in inflammation reduction (p = 0.74, I2 = 97%, MD = -0.14 [-0.96 – 0.68]) and pain reduction (p = 0.12, I_2 = 93%, MD = -1.1 [-2.48 – 0.28]) (Figure 3).

GRADE analysis

When evaluating the included studies, it was possible to observe that there is a very low certainty in the efficacy of serratiopeptidase to reduce trismus, pain and inflammation (Table 4).

DISCUSSION

Serratiopeptidase is a proteolytic enzyme, which is commonly used in various specialties such as surgery, orthopedics, otolaryngology, gynecology, and dentistry, due to its versatile properties, including antiedemic, antibiofilm, fibrinolytic, analgesic and anti-inflammatory effec[14]

The present study investigated the efficacy of

serratiopeptidase in its analgesic activity, it is related to the inhibition of bradykinin and other pain-inducing amines; inflammation, regulating inflammatory cytokines preventing chronic inflammation, and it also increases the viscosity of the accumulated fluid facilitating drainage, as it can modify the cell surface adhesion molecules that attract inflammatory cells to their target site; and trismus, due to the anti-inflammatory action of serratiopeptidase,[13,15] which decreases postoperative edema and thus prevents trismus after third molar extraction.[49,50]

As such, there was a statistically significant improvement in trismus after serratiopeptidase application compared to corticosteroids and NSAIDs. These results are in agreement with Sivaramakrishnan *et al.*,[19] Trismus usually improves progressively or disappears within 1 to 2 weeks after surgery.

Several factors can contribute to the development of lockjaw such as during the extraction of the mandibular third molar, on the buccal side the tendon of the muscle can be cut; low-grade infection following the administration of local anesthetic agents; multiple needle penetrations, especially if the needle injures the medial pterygoid during inferior alveolar nerve block; elevation of the flap beyond the external oblique ridge and when the patient injures the tongue or cheek under anesthesia, producing a reflex trismus.[31,32]

In the present study, serratiopeptidase was found to be ineffective in reducing pain and inflammation. However, the results from Sivaramakrishnan *et al.*,[19] are not in agreement. Because the main differences between the experimental and control groups were observed 3 days after surgery.
The certainty of results obtained from the current evidence in this study is very low, due to methodological limitations of the included studies, indicating that there is little confidence in the estimated effect and that it is very likely that the true effect is different from the estimate.

The present review has certain limitations such as: the high heterogeneity between the studies, the different sample sizes, the various pharmacological combinations, the lack of some data for the inclusion of some studies in the meta-analysis and the very low general confidence of the results of the studies included in the meta-analysis.
Therefore, the authors recommend taking the results of this study with caution, however, serratiopeptidase can be considered as an alternative drug in case of intolerance or contraindication to other drugs. In the future, more well-designed controlled clinical trials comparing them with other drugs are needed to clearly define the efficacy of this natural enzyme in third molar surgery.

CONCLUSION

Based on the evidence obtained in the present study, it can be concluded that ser-ratiopeptidase is effective in reducing trismus after third molar surgery, however, the certainty of this conclusion is very low.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest in relation to the published results.

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AUTHORS' CONTRIBUTIONS

Heber Arbildo-Vega: Planned the protocol for the systematic review, conducted the databases search, supervised the progress made, drafted the manuscript and revised the final manuscript.

Alfredo Rendón-Alvarado: Search in databases, selected articles and revised the final manuscript.

Tania Castillo-Cornock: Data extraction from the selected articles, collected the data, assessment of risk of bias of included studies and revised the final manuscript.

Fredy Cruzado-Oliva: Extracted the data from the selected articles, collected the data, assessed the risk of bias of included studies and revised the final manuscript.

Alex Vidal-Mosquera: Resolution of any discrepancy between the authors who evaluated the included studies, and revised the final manuscript.

Hernán Vásquez-Rodrigo: Drafted the manuscript and revised the final manuscript

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