Int. J. Oral Maxillofac. Surg. 2019; 48: 651–658
https://doi.org/10.1016/j.ijom.2018.07.028, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review And Meta-analysis

Oral Surgery

Is bromelain an effective drug for the control of pain and inflammation associated with impacted third molar surgery? Systematic review and meta-analysis

R. de A.C. Almeida, F. C. M. de Sousa Lima, B. C. do E. Vasconcelos
Department of Oral and Maxillofacial Surgery, University of Pernambuco – School of Dentistry (UPE/FOP), Tabatinga, Camaragibe, PE, Brazil

R. de A. C. Almeida, F. C. M. de Sousa Lima, B. C. do E. Vasconcelos: Is bromelain an effective drug for the control of pain and inflammation associated with impacted third molar surgery? Systematic review and meta-analysis. Int. J. Oral Maxillofac. Surg. 2019; 48: 651–658.

Abstract. The aim of this systematic review was to determine whether bromelain is an effective drug for the control of pain and inflammation associated with third molar surgery. Randomized, controlled clinical trials on the subject were identified through a systematic search of the literature using the PubMed/MEDLINE, Scopus, and Cochrane Library databases. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two independent, blinded reviewers selected studies based on the inclusion criteria. Divergences of opinion were resolved by consensus. A meta-analysis was performed for the outcomes pain and trismus and was based on the inverse variance method for continuous outcomes, considering the mean difference (MD) and corresponding 95% confidence interval (CI). A total of 186 articles were initially retrieved from the databases. After the different stages of the selection process, five articles reporting data for a total 252 patients remained and were included in the review. Bromelain proved to be effective at controlling postoperative pain at 48–72 h after surgery ($P = 0.03$; MD −0.89, 95% CI −1.70 to −0.09), but did not achieve a significant effect in comparison to the control group with regard to oedema or trismus.

Key words: third molar extraction; bromelain; oedema; trismus; pain; meta-analysis.

Accepted for publication 23 July 2018
Available online 14 September 2018

0901-5027/050651 + 08

Third molar surgery is normally associated with significant postoperative adverse effects that exert biological and social impacts. Pain, oedema, and trismus are the common symptoms of this procedure, the magnitude of which depends on the degree of impaction, difficulty of the surgical procedure, and the surgical technique employed[1,2].

The postoperative events related to the extraction of third molars are the result of the conversion of phospholipids into arachidonic acid due to the action of phospholipase A2 and the consequent conversion of this substance into prostaglandins, prostacyclins, and leukotrienes due to the action of cyclooxygenase and lipoxygenase. As well as sensitizing nociceptors, these chemical mediators of inflammation cause vasodilatation, with a consequent increase in cell permeability and oedema.

The administration of steroidal anti-inflammatory drugs, either pre-emptively or immediately following surgery, is an effective means by which to control these conditions and is widely practiced by oral surgeons[2,3]. The prescription of non-steroidal anti-inflammatory drugs (NSAIDs) to minimize these effects is also strongly indicated, especially for the pain associated with this procedure[4,5]. However, NSAIDs have numerous gastrointestinal, renal, and haematological side effects[5,6].

Efficient, safe, and natural medications with anti-inflammatory action and no side effects would be an excellent option for controlling pain, oedema, and trismus. Bromelain is a proteolytic enzyme extracted from pineapples (*Ananas comosus*) that was first used as an anti-inflammatory agent in 1957, generating considerable interest in the field of plastic surgery[7]. Administered orally, bromelain has been shown to have anti-inflammatory, anti-oedema, and analgesic properties related to its direct influence on inflammatory mediators, such as the blocking of bradykinin and modulation of the synthesis of prostaglandin[8]. It also exhibits fibrinolytic activity, which assists in the resorption of oedema fluid[8,9].

Considering the anti-inflammatory and analgesic effects of bromelain, as well as its clinical safety as a perioperative or postoperative medication, the aim of this systematic review of the literature was to evaluate the effectiveness of bromelain in the control of pain and inflammation associated with third molar surgery.

Materials and methods

Protocol and registration

This systematic review was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10]. The methods employed in this review have been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42017075973.

Eligibility criteria

The following was the guiding question of this review: Is bromelain effective at controlling pain, oedema, and trismus following the surgical extraction of impacted third molars?

The inclusion criteria were patients of any age submitted to the extraction of one or more impacted mandibular third molars; studies that compared the use of bromelain to a placebo or untreated control group; studies that measured the outcomes pain, oedema, and/or trismus (with no restrictions imposed on how the outcomes were measured); randomized controlled clinical trials; and articles published in English, with no restriction imposed regarding the year of publication.

The exclusion criteria were failure to describe the dose or time when the drug was administered; studies that compared the use of bromelain with other drugs without the presence of a placebo or untreated group; articles published in languages other than English; and cohort studies, case–control studies, laboratory studies, and studies for which the full article was not available.

Search strategy

Two independent reviewers (R.A. and F. L.) performed systematic searches of the PubMed/MEDLINE, Scopus, and Cochrane Library databases for articles published up to April 2017. The following key words were employed in the three databases: third molar and bromelain OR third molar and plant extracts OR third molar and phytotherapy OR third molar and oral hydrolytic enzymes OR impacted tooth and bromelain OR impacted tooth and plant extracts OR impacted tooth and phytotherapy OR impacted tooth and oral hydrolytic enzymes OR tooth extraction and bromelain OR tooth extraction and plant extracts OR tooth extraction and phytotherapy OR tooth extraction and oral hydrolytic enzymes. Hand searches were also performed in the principal journals in the field of oral and maxillofacial trauma and surgery: *International Journal of Oral and Maxillofacial Surgery*; *Journal of Oral and Maxillofacial Surgery*; *British Journal of Oral and Maxillofacial Surgery*; and *Journal of Cranio-Maxillo-Facial Surgery*.

The article selection process was conducted in two steps: (1) analysis of the titles and abstracts; and (2) full-text analysis. Two reviewers (R.A. and F.L.) performed the selection in an independent, blinded fashion based on the eligibility criteria. Divergences of opinion were resolved by consensus. When necessary, a third reviewer (B.V.) was consulted to make the final decision. Data were extracted from the selected articles and each article was evaluated with regard to the risk of bias. One author was contacted to obtain additional information to enable meta-analysis.

Data extraction

The data extraction was performed by one of the reviewers (R.A.) and checked by a second reviewer (F.L.). The following data were tabulated: demographic characteristics, characteristics of the study population, type of intervention, and outcomes of interest (pain, oedema, and trismus).

Risk of bias and methodological quality of included studies

The Cochrane risk of bias tool for randomized clinical trials was used to appraise the methodological quality of the studies included in this review. The following aspects were analyzed: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (unreported data), reporting bias (results reported in an incomplete or selective manner), and other bias (other threats related to the bias of origin).

Summary measures

Meta-analysis was based on the inverse variance method for continuous outcomes. Pain and trismus were the outcomes evaluated based on the mean difference (MD) and corresponding 95% confidence interval (CI). The MD was considered significant when $P < 0.05$. Review Manager 5.3 software (Cochrane group) was used for the meta-analysis. A fixed-effects model was to be used when the *P*-value related to heterogeneity was higher than 0.10 and a random-effects model was to be used when the *P*-value was less than 0.10[11].

Additional analyses

Inter-examiner agreement regarding pre-selected articles (after the analysis of the titles and abstracts) to be submitted to full-text analysis was determined using the kappa (κ) statistic.

Results

A total of 186 articles were retrieved from the three databases: 67 from PubMed/MEDLINE, 102 from Scopus, and 17 from the Cochrane Library. After the removal of duplicates, the titles and abstracts were analyzed based on the eligibility criteria. Nine articles were then included in the full-text analysis, four of which were excluded because they were not controlled trials. Thus, five articles were included in the systematic review and meta-analysis (Fig. 1)[2,5,7,12,13]. Inter-examiner agreement (κ) was calculated after the first step of the selection process, with a high level of agreement between the reviewers demonstrated for each database: $\kappa = 0.93$ for PubMed/MEDLINE, $\kappa = 0.92$ for Scopus, and $\kappa = 0.99$ for the Cochrane Library[14].

The study sample included in this review comprised a total of 252 patients aged 15 to 55 years; 86 were male and 98 were female (one study did not report the number of male and female subjects[7]). Different doses and dosing regimens of bromelain were used in the different studies. It was used as a postoperative medication in three studies[2,12,13], and as a perioperative medication in two studies[5,7]. The control group received a placebo drug in three studies[5,7,12] and was untreated in two studies[2,13]. With the exception of Bormann et al.[7], all researchers administered prophylactic[2] or postoperative[5,12,13] antibiotic therapy. The rescue drug given in all studies was paracetamol (acetaminophen), which was combined with codeine in the study by Ghensi et al.[2].

Table 1 displays the qualitative data of the studies included in this review. The quantitative analysis (meta-analysis) was performed for the outcomes pain (measured using a visual analogue scale (VAS) and based on the consumption of rescue analgesics) and trismus (difference between the maximum inter-incisal distance postoperative compared to baseline) (Table 2).

Pain

Pain was evaluated using a VAS in three of the five studies[5,7,12]. One study used the Postoperative Symptom Severity (PoSSe) scale[2] and one used a scoring scale[13]. The number of rescue pills was also used to evaluate pain.

In the qualitative analysis, the use of bromelain was favourable in the studies by Majid and Al-Mashhadani[5] and Ordesi et al.[13], whereas no significant difference in comparison to the control group was found in the other studies. The meta-analysis of pain was constructed based on studies that evaluated pain with a VAS and on studies that reported the number of rescue analgesics consumed. The meta-analysis for the pain outcome at the first postoperative evaluation (48–72 h) demonstrated a statistically significant difference favouring the use of bromelain in comparison to a placebo ($P = 0.03$; MD −0.89, 95% CI −1.70 to −0.09) (Fig. 2). Some evidence of a difference was also found for the 7-day evaluation, in which there was a tendency towards better pain control with the use of bromelain

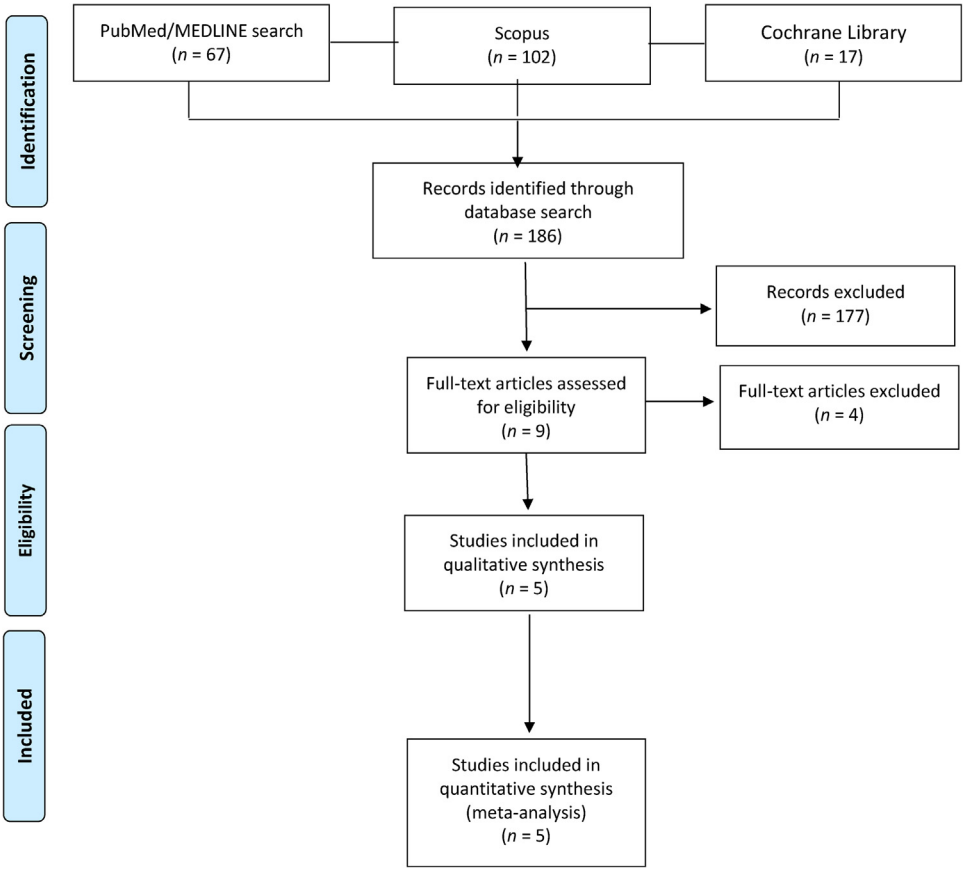

Fig. 1. Flow diagram of the search strategy.

Table 1. Qualitative results.

Authors and year	Number of patients	Groups	Sex Age (years)	Intervention	Control	Preoperative medication	Rescue analgesic	Outcomes	Effect of bromelain
de la Barrera-Núñez et al., 2014[12]	34	SG: 16 CG:18	17 M, 17 F 23.82 ± 3.9	Bromelain 50 mg, 3 × daily for 3 days and then 2 × daily for 4 days (total 7 days) Oral route Postoperative	Placebo	Amoxicillin–clavulanate 875 mg/125 mg every 8 h for 7 days	Paracetamol 500 mg	Pain Swelling Trismus	None; $P > 0.05$
Majid and Al-Mashhadani, 2014[5]	30	SG:15 CG: 15	12 M, 18 F 18–35	Bromelain 250 mg, 4 × daily for 4 days Oral route Perioperative	Placebo	Erythromycin 250 mg every 6 h for 5 days	Paracetamol 500 mg	Pain Swelling Trismus QOL	Positive; $P < 0.05$ None; $P > 0.05$ None; $P > 0.05$ Positive; $P = 0.007$
Ordesi et al., 2014[13]	80	SG:40 CG:40	35 M, 45 F 18–43	Bromelain 50 mg, 2 × daily for 7 days Oral route Postoperative	No treatment	Amoxicillin every 12 h for 6 days Paracetamol 1 g every 8 h	Paracetamol	Pain Swelling	Positive; $P < 0.01$
Bormann et al., 2016[7]	68	SG: 68 CG:68	NR 15–25	Bromelain 1000, 3000, or 4500 FIP units/day for 9 days Oral route Perioperative	Placebo	None	Paracetamol	Pain Swelling	None; $P > 0.05$ None; $P > 0.05$
Ghensi et al., 2017[2]	40	SG: 19 CG:21	22 M, 18 F 20–55	Bromelain 40 mg, 4 × daily for 6 days Oral route Postoperative	No treatment	2 g amoxicillin–clavulanate (prophylactic)	Paracetamol 500 mg + codeine 30 mg	Pain Swelling Trismus QOL	None; $P > 0.05$

CG, control group; F, female; FIP, Fédération Internationale Pharmaceutique; M, male; NR, not reported; QOL, quality of life; SG, study group.

($P = 0.08$; MD −0.32, 95% CI −0.67 to 0.04) (Fig. 3).

In the meta-analysis of pain based on the number of rescue analgesics consumed by the patients in the first 7 days of the postoperative period, no significant difference was found between the intervention group and the control group ($P = 0.80$; MD −0.09, 95% CI −0.82 to 0.63) (Fig. 4).

Oedema

Oedema was measured in different manners. The measurement of craniometric points was used in two studies[2,5]. Bormann et al.[7] measured volume using three-dimensional imaging. de la Barrera-Núñez et al.[12] and Ordesi et al.[13] used subjective measures (a VAS and a scoring scale, respectively). The use of bromelain was only favourable in the study by Ordesi et al.[13].

Trismus

Three studies measured trismus, which was based on the difference between the maximum inter-incisal distance postoperative (at 48–72 hours and at 7 days) and that at baseline[2,5,12]. These studies were included in the meta-analysis. None of the studies found that bromelain achieved a significant improvement in comparison to the control group. Moreover, the meta-analysis for trismus demonstrated no significant difference between the bromelain and control groups at the first postoperative evaluation (48–72 h) ($P = 0.09$; MD −2.64, 95% CI −5.68 to 0.39) (Fig. 5) or after 7 days ($P = 0.56$; MD −0.67, 95% CI −2.91 to 1.57) (Fig. 6).

Quality of life

Quality of life was evaluated using a validated questionnaire in two studies[2,5]. Majid and Al-Mashhadani found a better result in the bromelain group compared to the placebo group[5], whereas Ghensi et al. found no significant difference between the groups[2].

Risk of bias

Randomization and allocation were considered unsatisfactory in one study[13]. A high risk of bias was found with regard to blinding in the studies that used untreated patients as the control group[2,13]. One study failed to present all data (mean and standard deviation) for each group of interest

Table 2. Quantitative results; values are reported as the mean ± standard deviation.

Authors and year	Time of evaluation	Outcome							
		Pain		Swelling		Trismus (mm)		Number of rescue analgesics taken (7 days)	
		Bromelain	Control	Bromelain	Control	Bromelain	Control	Bromelain	Control
de la Barrera-Núñez et al., 2014[12,a]	Day 3	2.27 ± 2.5	2.0 ± 1.6	4.18 ± 2.81	5.19 ± 2.901	37.88 ± 10.7	37.78 ± 8.4	6.69 ± 1.352	5.78 ± 1.166
	Day 7	0.5 ± 0.6	0.72 ± 0.5	0.65 ± 0.651	0.88 ± 0.814	46.63 ± 8.0	43.72 ± 9.2		
Majid and Al-Mashhadani, 2014[5,b]	Day 1	2.4 ± 1.5	3.8 ± 1.6	8.8 ± 6.6	9.4 ± 4.4	13.8 ± 9.1	14 ± 8.5	3.4 ± 2.2	4.4 ± 2.0
	Day 3	1.3 ± 0.9	2.9 ± 1.9	4 ± 2.5	5.8 ± 5.2	6.6 ± 7.3	9 ± 7.1		
	Day 7	0.3 ± 0.7	1.5 ± 2.1	1.2 ± 1.9	2.9 ± 3.4	3.6 ± 6.5	4.1 ± 3.5		
Ordesi et al., 2014[13,c]	Day 2	1.75 ± 0.0776	1.775 ± 0.768	0.275 ± 0.452	0.550 ± 0.504	–	–	2.562 ± 0.609	2.588 ± 0.548
	Day 7	0.525 ± 0.506	0.875 ± 0.791	0.250 ± 0.439	0.400 ± 0.496	–	–		
Bormann et al., 2016[7,d]	Day 2	6.68 ± 7.11	7.26 ± 6.88	15.81 ± 9.99	18.14 ± 14.41	–	–	11.06 ± 8.14	11.82 ± 9.14
Ghensi et al., 2017[2,e]	Day 2	–	–	7.1 ± 5.6	9.1 ± 5.9	13.2 ± 7.5	17.4 ± 7.3	4.1 ± 4.3	5.8 ± 2.9
	Day 7	–	–	1.7 ± 2.2	1.9 ± 1.9	3.3 ± 4.5	5.2 ± 5.8		

VAS, visual analogue scale.

[a] Measurement methods (de la Barrera-Núñez et al.): pain by VAS; swelling by VAS.

[b] Measurement methods (Majid and Al-Mashhadani): pain by VAS; swelling by face measurements.

[c] Measurement methods (Ordesi et al.): pain by scoring scale; swelling by scoring scale.

[d] Measurement methods (Bormann et al.): pain by VAS; swelling by measurement of three-dimensional images, reported in millilitres.

[e] Measurement methods (Ghensi et al.): pain by postoperative symptom severity (PoSSe) scale; swelling by face measurements.

and was considered to have a high risk of bias with regard to incomplete outcome data and selective reporting[7]. Two studies performed outcome evaluations with an inadequate or subjective assessment tool and were considered to have a high risk of 'other bias' (Fig. 7)[12,13].

Discussion

This systematic review only included randomized, controlled clinical trials to test the null hypothesis that bromelain is not superior to a placebo or the absence of treatment with regard to pain, oedema, and trismus following the surgical removal of impacted mandibular third molars.

The consequences of third molar surgery stem from the inflammatory process that follows tissue injury, and drugs that inhibit phospholipase A2 and block or modulate the synthesis of inflammatory mediators, such as prostaglandins, prostacyclins, bradykinin, and leukotrienes, are important for the control of the pain, oedema, and trismus associated with such procedures. Therefore, bromelain has been studied as an alternative to glucocorticosteroids and NSAIDs.

Based on the qualitative analysis, the null hypothesis was rejected in only two of the five studies for the pain outcome[5,13] and one for the oedema outcome[13], with statistically significant results favouring the use of bromelain. In contrast, the null hypothesis was accepted in the other studies. Based on the quantitative analysis, the null hypothesis was rejected for the pain outcome at the 48–72-h evaluation when measured using the VAS, but with no statistically significant difference when evaluated based on the number of rescue analgesics consumed by the patients.

The meta-analysis for the pain outcome demonstrated that bromelain was statistically superior to a placebo, making it an alternative to routinely prescribed medications such as NSAIDs and analgesics. The three studies included in this meta-analysis performed comparisons between an experimental group (bromelain) and a placebo control group[5,7,12], which certainly led to more reliable results without overestimating the findings in the experimental group.

Although the meta-analysis for the trismus outcome tended to favour bromelain, the difference in comparison to the control group was non-significant. In this evaluation, an overestimation of the results could have occurred, as one of the studies included in the analysis had a control group that received no intervention[2], giving it a

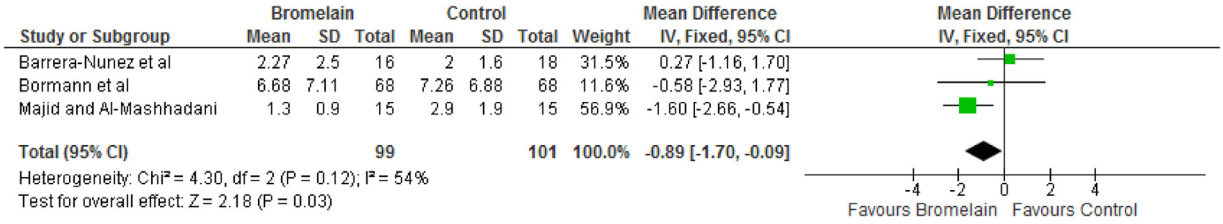

Fig. 2. Evaluation of pain at 48–72 hours (VAS).

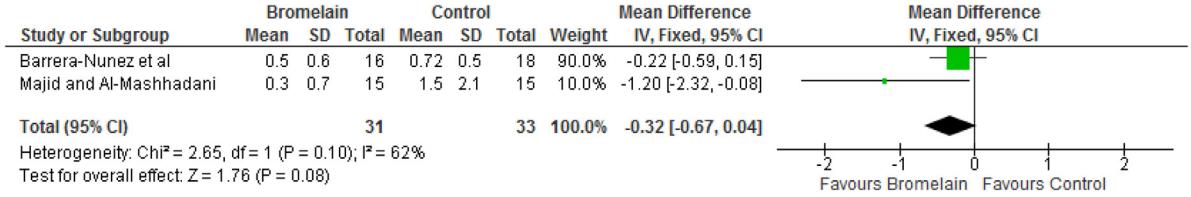

Fig. 3. Evaluation of pain at 7 days (VAS).

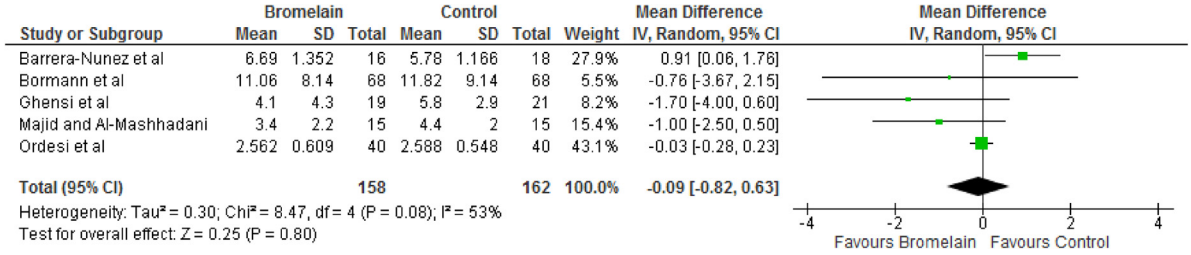

Fig. 4. Evaluation of pain/rescue analgesic consumption at 7 days.

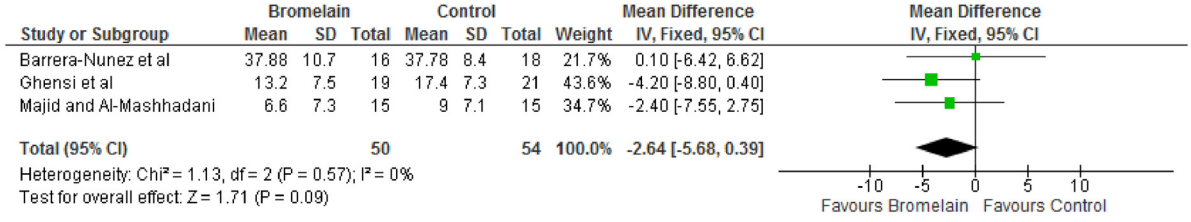

Fig. 5. Evaluation of trismus at 48–72 hours.

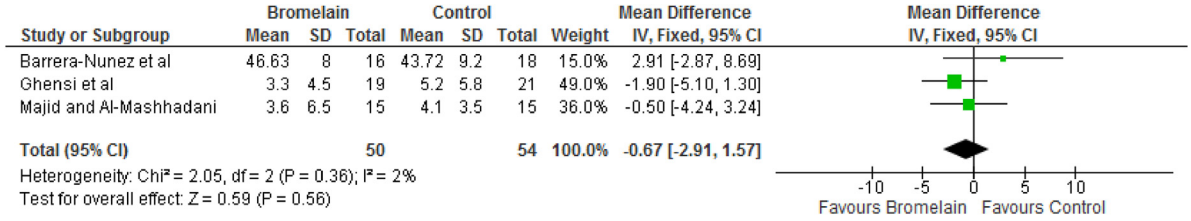

Fig. 6. Evaluation of trismus at 7 days.

high risk of bias with regard to the criterion of blinding the participants.

A meta-analysis for the outcome oedema was not viable due to the different ways in which this was measured in the different studies, such as the use of subjective scales, distance measurements between craniometric points on the face, and the three-dimensional imaging of volume in the preoperative and postoperative periods. Although less oedema and greater regression of oedema were found in the experimental group compared to the control group, the difference was only statistically significant in one study[13]. However, the study in question was considered to have a high risk of bias due to the use of a subjective assessment tool that was not appropriate for the evaluation of this outcome, as well as the fact that the control group was untreated. These biases could

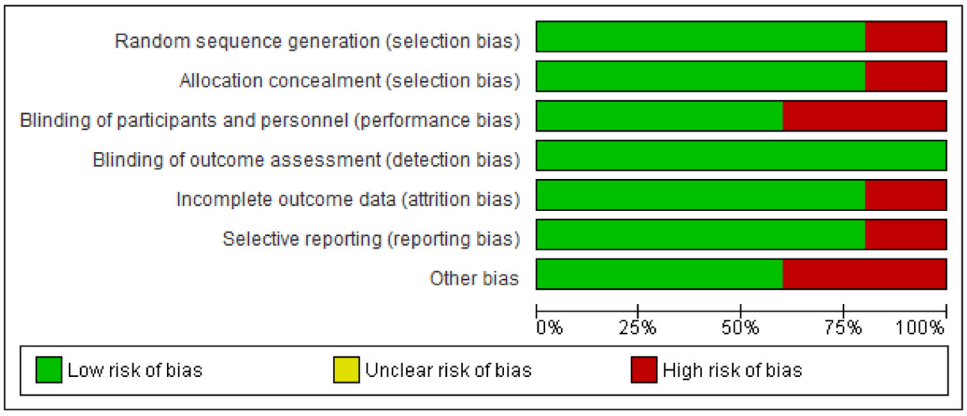

Fig. 7. Risk of bias graph.

certainly have led to an overestimation of the effect found in the experimental group.

Among the limitations of this systematic review is the lack of clinical trials on the use of bromelain as a medication for patients submitted to the surgical removal of impacted mandibular third molars. The use of a control group not submitted to any type of intervention is another limitation, as this could influence the response of the patients and lead to an overestimation of the effects in the intervention group.

The majority of studies included in this review limited the description of the population to patients submitted to the surgical removal of impacted third molars, without specifying the degree of impaction or degree of surgical difficulty. The operating time is the variable most often correlated with surgical difficulty, but was also not mentioned in the articles. This renders an analysis of the real anti-inflammatory effect of bromelain in cases of greater or lesser surgical trauma and consequently greater or lesser associated inflammation unviable.

There was no consensus regarding the dose of bromelain used. One study used a dose of 100 mg/day (50 mg twice daily) and reported results favouring bromelain over a placebo[13], and another used 1000 mg/day (250 mg four times daily) and found a favourable result for bromelain over the placebo only for one outcome (pain)[5]. Furthermore, Bormann et al. used doses of 1000, 3000, and 4500 FIP/day, with no difference among the doses or in comparison to a placebo[7]. They stated that there is no reason to use a dose of bromelain beyond 1000 FIP/day because it does not bring any additional benefit[7]. Further investigations are needed to define the most effective dose of bromelain.

Ghensi et al. performed a comparison of four groups: control, bromelain, dexamethasone, and dexamethasone combined with bromelain[2]. Only two of these groups (control and bromelain) were considered of interest for the present systematic review and meta-analysis, and no significant difference was found between the two groups. However, when using a single pre-emptive dose of dexamethasone combined with the postoperative use of bromelain, a statistically significant difference was found in comparison to both the control group and the bromelain group.

Considering the scientific evidence for the use of a single dose of a corticosteroid employed in third molar surgery and the results of the present systematic review, which demonstrated improved control of postoperative pain and a tendency towards benefits of bromelain in reducing oedema and trismus, it may be suggested that bromelain can be used an alternative to NSAIDs, especially with regard to the control of pain, but that it cannot cover the benefits provided by the use of glucocorticoids.

Further crossover and placebo-controlled clinical trials should compare glucocorticoids combined with bromelain to a placebo group and to a second experimental group involving the glucocorticoid combined with NSAIDs or nociceptor-depressing analgesics for a better evaluation of the anti-inflammatory and analgesic activity of bromelain.

Bromelain appears to be an effective medication for the control of postoperative pain and probably for the control of oedema and trismus associated with the surgical removal of impacted third molars, as an adjuvant to a pre-emptively used corticosteroid. Bromelain could be used as a substitute for NSAIDs, thereby eliminating patient exposure to the adverse effects associated with these medications.

Funding

No source of funding.

Competing interests

No competing interests.

Ethical approval

Not applicable.

Patient consent

Not applicable.

Acknowledgements. The authors are grateful to the Brazilian fostering agency Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; Coordination for the Advancement of Higher Education Personnel) and to the authors de la Barrera-Núñez et al. for providing additional data not reported in their article to enable the meta-analysis.

References

1. de Santana-Santos T, de Souza-Santos JA, Martins-Filho PR, da Silva LC, de Oliveira E, Silva ED, Gomes AC. Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. *Med Oral Patol Oral Cir Bucal* 2016;**2013**(18):e65–70. http://dx.doi.org/10.4317/medoral.18039.
2. Ghensi P, Cucchi A, Creminelli L, Tomasi C, Zavan B, Maiorana C. Effect of oral administration of bromelain on postoperative discomfort after third molar surgery. *J Craniofac Surg* 2016;**2017**(28):e191–7. http://dx.doi.org/10.1097/SCS.0000000000003154.
3. Moraschini V, Hidalgo R, Porto Barboza E. Effect of submucosal injection of dexamethasone after third molar surgery: a meta-analysis of randomized controlled trials. *Int J Oral Maxillofac Surg* 2016;**2016**(45):232–40. http://dx.doi.org/10.1016/j.ijom.2015.09.008.

4. Seymour RA, Walton JG. Pain control after third molar surgery. *Int J Oral Surg* 1984;**13**:457–85.
5. Majid OW, Al-Mashhadani BA. Perioperative bromelain reduces pain and swelling and improves quality of life measures after mandibular third molar surgery: a randomized, double-blind, placebo-controlled clinical trial. *J Oral Maxillofac Surg* 2016;**2014**(72):1043–8. http://dx.doi.org/10.1016/j.joms.2013.12.035.
6. Little JW, Falace DA, Miller CS, Rhodus NL. *Dental management of the medically compromised patient*. Fifth edition. St Louis, MO: Mosby; 1997.
7. Bormann KH, Weber K, Kloppenburg H, Staude P, Koch A, Meiser P, Gellrich NC. Perioperative bromelain therapy after wisdom teeth extraction — a randomized, placebo-controlled, double-blinded, three-armed, cross-over dose-finding study. *Phytother Res* 2016;**2016**(30):2012–9. http://dx.doi.org/10.1002/ptr.5707.
8. Bromelain. *Altern Med Rev* 1998;**3**:302–5.
9. MacKay D, Miller AL. Nutritional support for wound healing. *Altern Med Rev* 2003;**8**:359–77.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2016;**2009**(151):264–9. http://dx.doi.org/10.7326/0003-4819-151-4-200908180-00135.
11. Egger M, Smith GD. Principles of and procedures for systematic reviews. In: Egger M, Smith GD, Altman AG, editors. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books; 2003. p. 23–42.
12. de la Barrera-Núñez MC, Yáñez-Vico RM, Batista-Cruzado A, Heurtebise-Saavedra JM, Castillo-de Oyagüe R, Torres-Lagares D. Prospective double-blind clinical trial evaluating the effectiveness of bromelain in the third molar extraction postoperative period. *Med Oral Patol Oral Cir Bucal* 2016;**2014**(19):e157–62. http://dx.doi.org/10.4317/medoral.19105.
13. Ordesi P, Pisone L, Nannei P, Macchi M, Borloni R, Siervo S. Therapeutic efficacy of bromelain in impacted third molar surgery: a randomized controlled clinical study. *Quintessence Int* 2016;**2014**(45):679–84. 103290/j.qi.a32237.
14. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.

Address:
Belmiro Cavalcanti do Egito Vasconcelos
Department of Oral and Maxillofacial Surgery
University of Pernambuco – School of Dentistry (UPE/FOP)
Av. General Newton Cavalcanti
1650
Tabatinga
Camaragibe
PE 54.756-220
Brazil
E-mail: belmiro@pesquisador.cnpq.br