Journal of Dental Sciences 19 (2024) 885–893

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jds.com

Original Article

Can botulinum toxin injection alleviate the pain of bruxism? A Bayesian network analysis and a single-arm analysis

Ao-bo Zhang [a,b], Jian-yun Zhang [a,b], Xia Zhou [c], Li-sha Sun [b,d*], Tie-jun Li [a,b**]

[a] *Department of Oral Pathology, Peking University School and Hospital of Stomatology & National Center of Stomatology & National Clinical Research Center for Oral Diseases & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices, Beijing, China*
[b] *Research Unit of Precision Pathologic Diagnosis in Tumors of the Oral and Maxillofacial Regions, Chinese Academy of Medical Sciences (2019RU034), Beijing, China*
[c] *Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China*
[d] *Central Laboratory, Peking University School and Hospital of Stomatology, Beijing, China*

Received 21 July 2023; Final revision received 31 July 2023
Available online 22 August 2023

KEYWORDS
Botulinum toxin;
Bruxism;
Bayesian network meta-analysis;
Pain

Abstract *Background/purpose:* There is inconsistent evidence regarding whether the botulinum toxin A (BTA) injection can relieve pain caused by bruxism. This study aimed to estimate the efficiency of BTA injection in relieving pain caused by bruxism at different follow-up periods.

Materials and methods: Five electronic databases were searched from 2005 to 2022 using search terms related to botulinum toxin and bruxism. Only controlled clinical trials were included. Two investigators reviewed each article and discussed any disagreements until a consensus was reached. Pain outcomes as evaluated by the visual analogue scale (VAS) were subjected to single-arm and Bayesian network meta-analyses. Pooling data were measured by a random-effects model.

Results: Eleven studies with a total of 365 bruxism patients were included. According to the single-arm analyses of the pooled data, the reduction in bruxism-related pain after BTA injection measured 4.06 points (95% CI = 3.37 to 4.75) on the VAS, and the pain relief was significant in the first 6 months after treatment ($P < 0.01$). According to the Bayesian analysis, BTA also resulted in significantly greater pain relief than oral splinting (mean difference

* Corresponding author. Central laboratory & Research Unit of Precision Pathologic Diagnosis in Tumors of the Oral and Maxillofacial Regions, Peking University School and Hospital of Stomatology, No. 22, Zhongguancun South Avenue, Haidian District, Beijing 100081, PR China.
** Corresponding author. Department of Oral Pathology, Peking University School and Hospital of Stomatology, No. 22, Zhongguancun South Avenue, Haidian District, Beijing 100081, PR China.
E-mail addresses: zhouxia@pkuss.bjmu.edu.cn (X. Zhou), lisa_sun@bjmu.edu.cn (L.-s. Sun), litiejun22@vip.sina.com (T.-j. Li).

https://doi.org/10.1016/j.jds.2023.08.001

(MD), −1.5; 95% credible interval (CrI) = −2.7 to −0.19) or saline injection (MD, −3.3; 95% CrI = −6.2 to −0.32).
Conclusion: BTA significantly relieves the pain of bruxism for 6 months after injection, and its therapeutic efficacy was higher than that of oral splinting. Nevertheless, further long-term follow-up randomized controlled trials comparing BTA with other management or drugs are warranted.

Introduction

Bruxism is a type of abnormal muscle group activity that causes a series of irregular mandible movements including thrusting or bracing of the jaw as well as grinding or clenching of the teeth.[1] Bruxism is grouped into two categories based on its place in the circadian cycle: awake bruxism (bruxism occurring during wakefulness) and sleep bruxism (bruxism occurring during sleep). These abnormal movements probably cause other disorders, such as functional abnormalities in the temporomandibular joint,[2] low-quality sleep, headache,[3] myofascial pain,[4,5] and tooth wearing due to overloading of the stomatognathic system. Because of the above complications, pain symptoms have become a major concern for bruxism patients.[6] There is no consensus on the aetiology of the bruxism. Some authors believed that psychological factors, occlusal disturbances, and abnormal morphology may increase the risk of bruxism, but there is no conclusive evidence supporting these points thus far.[7] The prevalence of bruxism in the general population is 22.1%—31.4,[8] with a female predominance, and all age groups are affected. Additionally, the more developed the geographical location, the higher the incidence.[9]

For the treatment of bruxism, patients prefer relatively conservative treatments, such as oral appliances, cognitive-behavioural approaches and psychosocial interventions, as they are noninvasive and cost little. However, there have not been sufficient studies to set a specific guide for the bruxism management, and these interventions require good compliance in order to be effective.[10,11] Pharmacological approaches, such as botulinum toxin, clonazepam, clonidine, propranolol and amitriptyline,[12,13] are more effective and less dependent on compliance than conservative treatments, but they require patients to have no allergies or other stress reactions to these drugs and are sometimes limited by contraindication to their application. Surgical treatment for bruxism may be the least acceptable option for both patients and doctors because it can cause damage to the surrounding normal tissues, and a series of strict indications must be met before surgery is performed.

Botulinum toxin (BTA) was first found in poorly prepared foods such as blood sausages and has been recognized as a lethal substance for many centuries, causing painful, secretory dysfunction, and unfavorable cosmetic changes.[14] Until 1981, BTA was applied therapeutically by injection into the external oculomotor muscles to correct strabismus caused by neuromuscular disorder.[15] Thereafter, the perception of BTA changed completely when it was first approved by the FDA for the clinical applications in 1989.[16] In terms of composition sources, BTA is a type of endotoxin secreted from the anaerobic botulinum, and it can reduce muscle contraction by constraining the connectivity of neuromuscular transmission.[17] Therefore, some researchers suggested that BTA could be used to manage bruxism by alleviating contractions of masticatory muscles. BTA has seven structurally similar but immunologically distinct types, designated A, B, C, D, E, F and G subtypes marked by the capitals, of which type A (BTA) is the most widely used.

In this study, we performed a single-arm and Bayesian network meta-analyse to evaluate the efficacy of BTA-A injection in relieving the pain caused by bruxism. We hypothesized that BTA-A injection could be a reliable and stable means for managing bruxism at any follow-up period. To our knowledge, this study is the largest to date on this subject and the first undertaken to investigate the therapeutic efficacy of BTA for pain relief in bruxism via two analysis methods. This study allows us to understand the potential therapeutic role of BTA in bruxism, providing a reliable option for relieving the pain caused by bruxism.

Materials and methods

Search process for literatures

A literature search was undertaken in the Web of Science, Medline (PubMed), Embase and Cochrane Library databases to identify full-text articles published from 2005 to 2022. The search keywords mainly include: "Botulinum Toxins" and "Bruxism". There were no restrictions on the language of publication. In addition, references of probably related articles from the included studies were also screened. Each specific step of the Web of Science and Medline search processes are shown in the **Supplement-Appendix** as examples. Two investigators (the 1st and 2nd authors), working independently, screened each abstract against the inclusion criteria; disagreements resulted in inclusion at this stage. Full-text records for the relevant abstracts were retrieved, and each record was independently reviewed by

2 investigators (the 1st and 2nd authors). Two investigators then used standardized forms to extract the study endpoints.

Inclusion and exclusion criteria

The inclusion criteria for the studies to be considered in this study were as follows:

(1) Articles related to human clinical trials, including observation studies, retrospective or prospective randomized controlled trials (RCTs), and cohort studies, that evaluated the efficacy of BTA injection in relieving bruxism-related pain.
(2) Trials whose subjects were adults diagnosed as bruxism.
(3) Outcomes recording muscle pain severity in patients with bruxism at different follow-up periods after management.

The exclusion criteria were as follows:

(1) Reviews or systematic reviews, meta-analysis, case reports, and meeting abstracts;
(2) Trials involving animal subjects;
(3) Trials that did not report key data regarding pain severity in bruxism.

Quality and risks-of-bias assessment for the included articles

Quality and risks-of-bias assessments for the RCTs were performed according to the Cochrane Collaboration notebook and guide,[17] which includes 7 items: blinding of personnel and participants, selection bias, random sequence generation, blinding of outcome assessment, attrition bias, reporting bias, and other biases. For non-RCTs, the non-RCT of Interventions tool was used to assess the quality and risk of bias.[18] This tool also includes 7 items: intervention classification, confounding factors, deviations from intended intervention, selective reporting, detection bias, selection bias, and selective bias. Each domain was ranked as having a low, moderate, significant, or critical risk of bias. For each of the 7 items, two reviewers (Author 1st and 2nd) selected one of three options, including low risk, high risk and unclear risk. "Low risk" was give one point, while high risk and unclear risk were given zero points. The total score was considered to reflect the quality of each study (0–2: low quality; 3–5: moderate quality; 6–7: high quality).

Data collection

Using a data collection form created after including literatures, two reviewers independently extracted the data from the included studies. The following data were collected: the country of the study; authors and year of publication; age; sample size; study design; intervention methods for bruxism patients; BTA injection dosage and position; outcomes of pain on bruxism; and the follow-up period.

Statistical methods

Data analysis was performed with R version 4.2.0. The package "meta" (version 6.0) was used to perform the single-arm analysis, and the packages "gemtc" (version 1.01) and "rjags" (version 4.13) were used to perform the Bayesian network meta-analysis. A random-effects model was used to analyse all estimates, as variations between studies could exist in the real world. For the single-arm analysis, the mean differences (MD) with 95% confidence intervals (CIs) were used to assess the changes in pain scores. Statistical heterogeneity was defined by the I^2 test at a $= 0.1$. We performed a subgroup analyses for different follow-up periods. For the Bayesian network meta-analysis, network plots were generated to illustrate the network geometry of different management strategies for bruxism. Odds ratios (ORs) with 95% credible interval (CrIs) were created to show all results,[19] which were visually pooled in forest plots. The relative rank probabilities of all management strategies for bruxism were calculated to determine whether BTA injection was the most effective treatment.[20] For hypothesis testing, statistical significance was defined by $P < 0.05$.

Results

Characteristics of the included studies

The search procedure was mapped out according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement; a search flowchart is shown in Fig. 1. A total of 495 records were identified from four electronic databases (PubMed, Web of science, Embase and Cochrane Library), of which 197 studies were duplicates. Then, 287 studies were screened out on the bases of irrelevant titles and abstracts. Ultimately, eleven studies[21–31] containing a total of 365 patients were included: all eleven studies were included in the single-arm analysis, and the seven that were RCTs were included in the Bayesian network meta-analysis. The characteristics of the included studies are shown in Table 1. The quality assessment of the seven RCTs and four non-RCTs is presented in Fig. 2 and in the last column of Table 1, respectively.

Single-arm meta-analysis

Ten studies included in the single-arm meta-analysis reported the efficacy of BTA in relieving bruxism-related pain evaluated by a visual analogue scale (VAS) between the pre-injection and post-injection timepoints. We divided them into three groups based on the follow-up timepoints, namely, the 1st, 3rd and 6th months. A forest plot containing 26 records (Fig. 3) showed that the VAS score of bruxism-related pain decreased by 4.06 (95% CI, 3.37 to 4.75) after injection of BTA, and the pooled results in the subgroups (Fig. 3) showed that 4.28 (95% 3.09 to 5.47, follow-up $\leq$ 3months), 3.87 (95%CI 2.60 to 5.14, 3 $<$ follow-

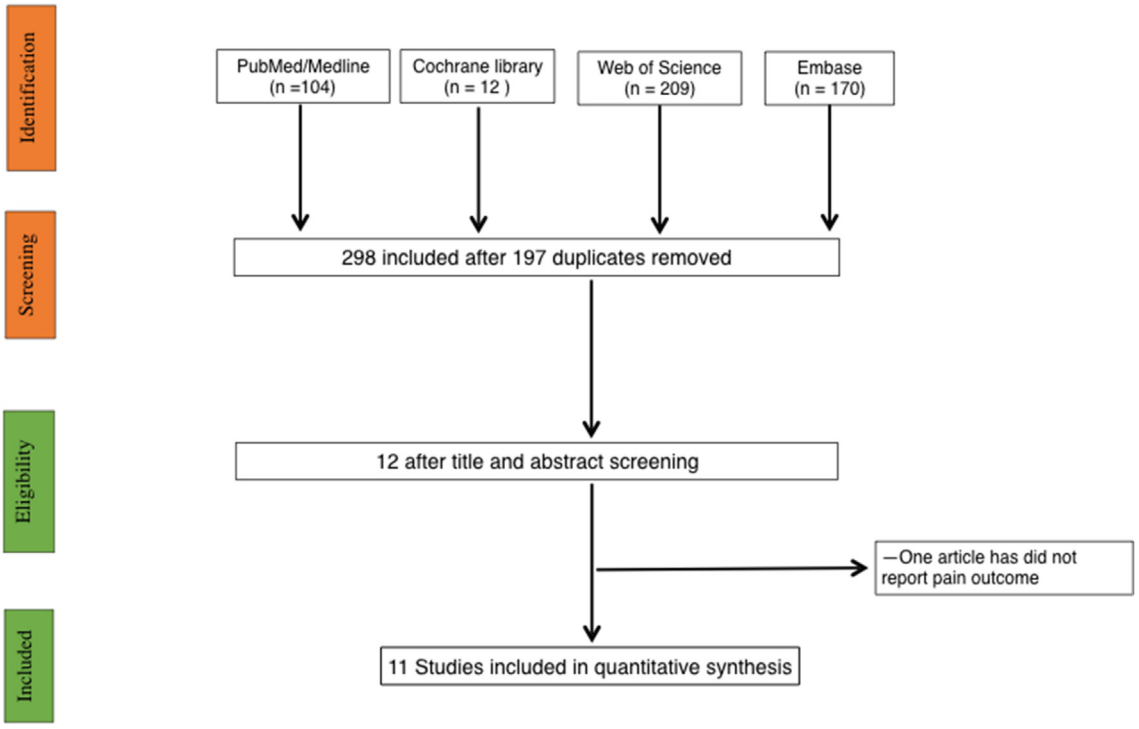

Figure 1 Flow diagram of the search process.

Table 1 Characteristics of the included studies.

Study	Years	Study design	Sample Size (M, F)	Age (Mean ± SD or range)	Intervention vs. control	Injection positon	BTX-A Dosage (U)	Outcomes	Follow-up length	Quality score
Guarda et al.[21]	2007	RCT	20 (10, 10)	25 - 45 y	BTX-A vs. Saline	MM and TM	MM: 60 TM: 40	Pain (VAS)	6 months	NA
Al-Wayli et al.[22]	2017	RCT	50 (0, 10)	45.5 ± 10.8 y	BTX-A vs. Oral splinting	MM	MM: 40	Pain (VAS)	1 year	NA
Jadhao et al.[24]	2017	RCT	24 (NR)	20 - 35 y	BTX-A vs. Saline	MM and TM	MM: 60 TM: 40	Pain (VAS)	6 months	NA
Yurttutan et al.[26]	2019	RCT	73 (28, 45)	30.5 ± 9.95 y	BTX-A vs. Saline	MM and TM	MM: 30 TM: 15	Pain (VAS)	6 months	NA
Ondo et al.[25]	2018	RCT	23 (3, 19)	47.4 ± 16.9 y	BTX-A vs. Saline	MM and TM	MM: 120 TM: 80	Pain (VAS)	2 months	NA
Al-Wayli et al.[29]	2021	RCT	40 (16, 24)	30.9 ± 31 y	BTX-A vs. Saline	MM	MM: 20	Pain (VAS)	6 months	NA
Kaya et al.[28]	2021	RCT	40 (7, 33)	18 - 45 y	BTX-A vs. Oral splinting	MM	MM: 24	Pain (VAS)	6 months	NA
Asutay et al.[23]	2017	RS	25 (0, 25)	35.84 ± 8.41 y	BTX-A	MM	MM: 20	Pain (VAS)	6 months	6, HQ
Hosgor et al.[27]	2020	RS	44 (8, 36)	35.7 ± 12.66 y	BTX-A	MM and TM	MM: 50 TM:33.33	Pain (VAS)	6 months	6, HQ
Kef et al.[30]	2021	PS	37 (15, 22)	34 ± 9.13 y	BTX-A	MM and TM	MM: 20; TM: 25	Pain (VAS)	6 months	5, MQ
Silva et al.[31]	2022	PS	20 (4, 16)	34 ± NR y	BTX-A	MM and TM	100	Pain (VAS)	6 months	6, HQ

Note/Abbreviation: RCT, randomised controlled trials; M, male; F, female; U, units; BTX-A, Botulinum toxin A; MM, masseter muscle; TM, temporalis muscle; NR, no records; NA, not available; NR, no record; HQ, high quality; MQ, moderate quality.

up $<$ 6 months) and 3.99 (95%CI 2.76 to 5.23, follow-up $\geq$ 6months). The line chart (Fig. 4) shows significant pain reduction at the 1st, 3rd and 6th months after injection of BTA compared with the pre-injection timepoint ($P < 0.01$).

Bayesian meta-analysis

Seven RCTs articles included in the Bayesian meta-analysis to evaluate pain reduction in the BTA, oral-splint and saline

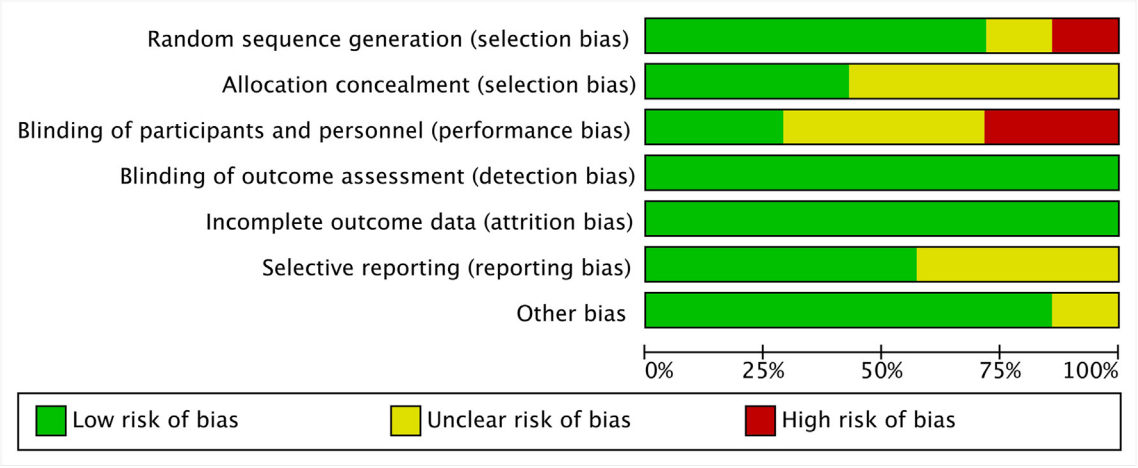

Figure 2 Risk of bias and quality assessment for RCTs on summary.

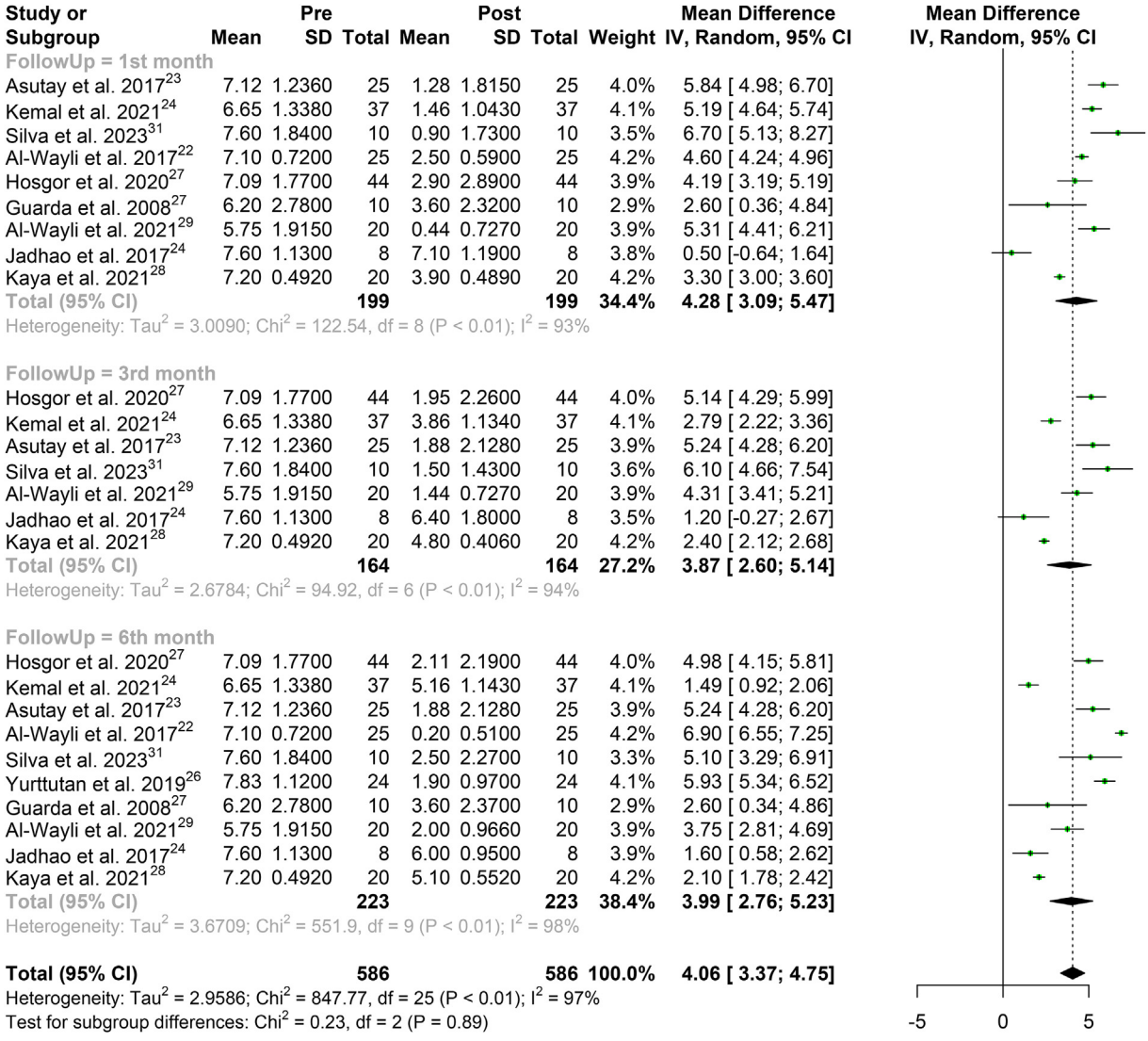

Figure 3 Forest plot of bruxism pain relief evaluated by VAS score. Pre: pre-injection; Post: post-injection; MD: mean difference; 95% CI: confidence interval.

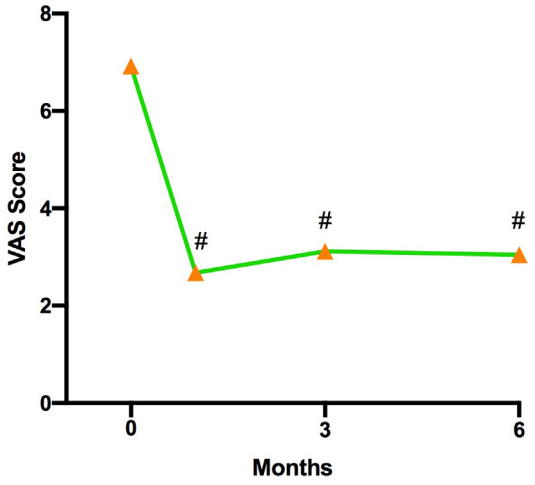

Figure 4 Line chart indicating tendency of VAS score at pre-injection, 1st, 3rd and 6th month.

placebo groups. The structure of the different management strategies for bruxism is shown in Fig. 5. The results of the Bayesian meta-analysis indicated that BTA injection was significantly more effective than oral splinting (MD, −1.5; 95% CrI, −2.7 to −0.19, Fig. 6A) or saline (MD, −2.4; 95% CrI, −3.2 to −1.1, Fig. 6A) at follow-up 3rd month. While at follow-up 1st and 6th month (Fig. 6A, 1st and 6th month), the bruxism pain reduction of BTA injection were slightly higher than that of oral splinting (MD, −0.67; 95% CrI, −1.9 to 0.57, 1st month; MD, −1.7; 95% CrI, −4.5 to −1.2, 6th month) although these differences were not statistically significant, and significantly higher than that of saline (MD, −1.7, 95% CrI, −2.9 to −0.67, 1st month; MD, −3.3, 95% CrI, −6.2 to −0.32, 6th month). Additionally, the ranking probability plot (Fig. 6B) suggests that BTA injection is most likely to be the best approach (80.73%, 98.09% and 81.05%, Fig. 6B) at any follow-up period.

In addition, the shrink factor for each comparison was nearly 1.0 and showed no instability after 40 000 iterations on a Gelman convergence plot (Fig. 7), which indicated the result possessed a reliable convergence.

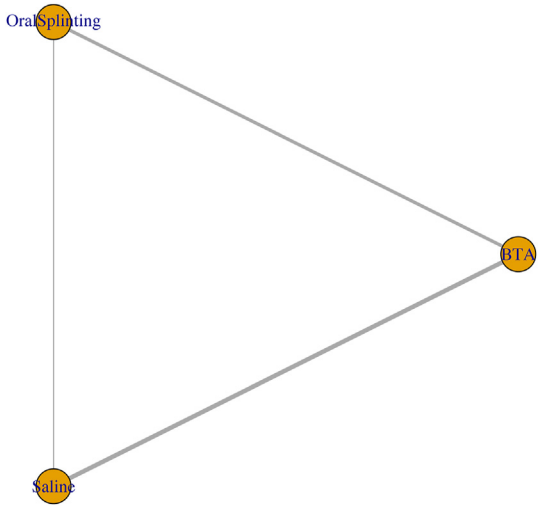

Figure 5 Network plots of different managements for bruxism patients. BTA: botulinum toxic A.

Discussion

BTA relieves bruxism-related pain through several mechanisms. Several studies have indicated that neurotransmitters release can be suppresed by BTA to achieve pain relief[32]; for example, the substance P from the dorsal root ganglion can be blocked,[6] limiting the resulting pain-related amount calcium signaling. Furthermore, BTA injections can reduce the muscle contraction by reducing the extracellular concentration of acetylcholine in the motor nerve terminals, which induces muscle relaxation, resulting in a decrease in pain levels.[33] Therefore, we deduced that the BTA injection would significantly relieve the severity of pain caused by bruxism. In this study, we found significant relief of bruxism-related pain at every timepoint after injection of BTA compared with the pre-injection timepoint, and BTA maintained stable efficacy in the relief of bruxism-related pain for six months. Furthermore, BTA reduced the pain score by 4.06 compared with its pre-injection value (Fig. 3), which means that BTA injection into the masticatory muscles could relieve the initial severe or very severe pain to mild pain (Fig. 4). Regarding the safety of BTA, several studies found no significant adverse events and sometimes no adverse effects at all during the treatment of bruxism.[6]

Occlusal splint therapy is the traditional and first-line choice for the treatment of bruxism in the clinical practice of dentistry due to its relatively low cost and easy application; in contrast, BTA is costly to produce and requires repeated injection. However, wearing occlusal splints can cause an uncomfortable foreign-body sensation in in the mouth and trigger the gag reflex. Additionally, the therapeutic efficacy of occlusal splinting is intermittent, as it is difficult to wear the device for the whole day, whereas BTA injection can generate a sustained therapeutic efficacy against bruxism for at least six months. Based on this information about BTA and oral splinting, we deduced that BTA relieved bruxism-related pain more effectively than oral splinting. This Bayesian network meta-analysis suggested that BTA injection was more effective than oral splinting and saline injection in reducing pain levels in bruxism patients at all follow-up timepoints.

There are several possible explanations for the heterogeneity observed in this study. The different injection doses, positions, and pain score evaluation methods were not completely consistent among the included studies. The selection of BTA injection sites to manage bruxism is controversial, as some researchers believe that multiple muscles are activated during bruxism events,[34] while others believe that only the masseter muscles are involved and that they should therefore be the primary or even the only injection sites.[22] The doses applied in the included studies ranged from 20 to 120 U, and some articles failed to accurately record whether consistent doses were used bilaterally. Different dosages would be expected to alter the treatment effectiveness of bruxism treatment, but in practive, the influence is not obvious; BTA can be fully effective at low doses. Finally, Jadhao et al.[24] applied only

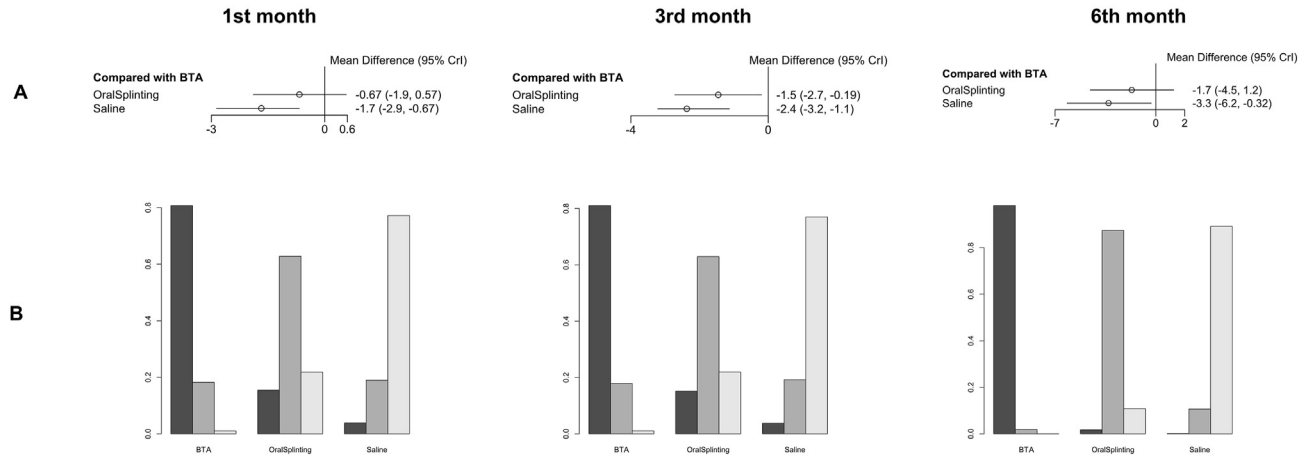

Figure 6 Forest plots of different comparisons in network meta-analysis (A) and Ranking probabilities of all managements for bruxism (B). BTA: botulinum toxic A; MD, mean difference; CrI, credible interval.

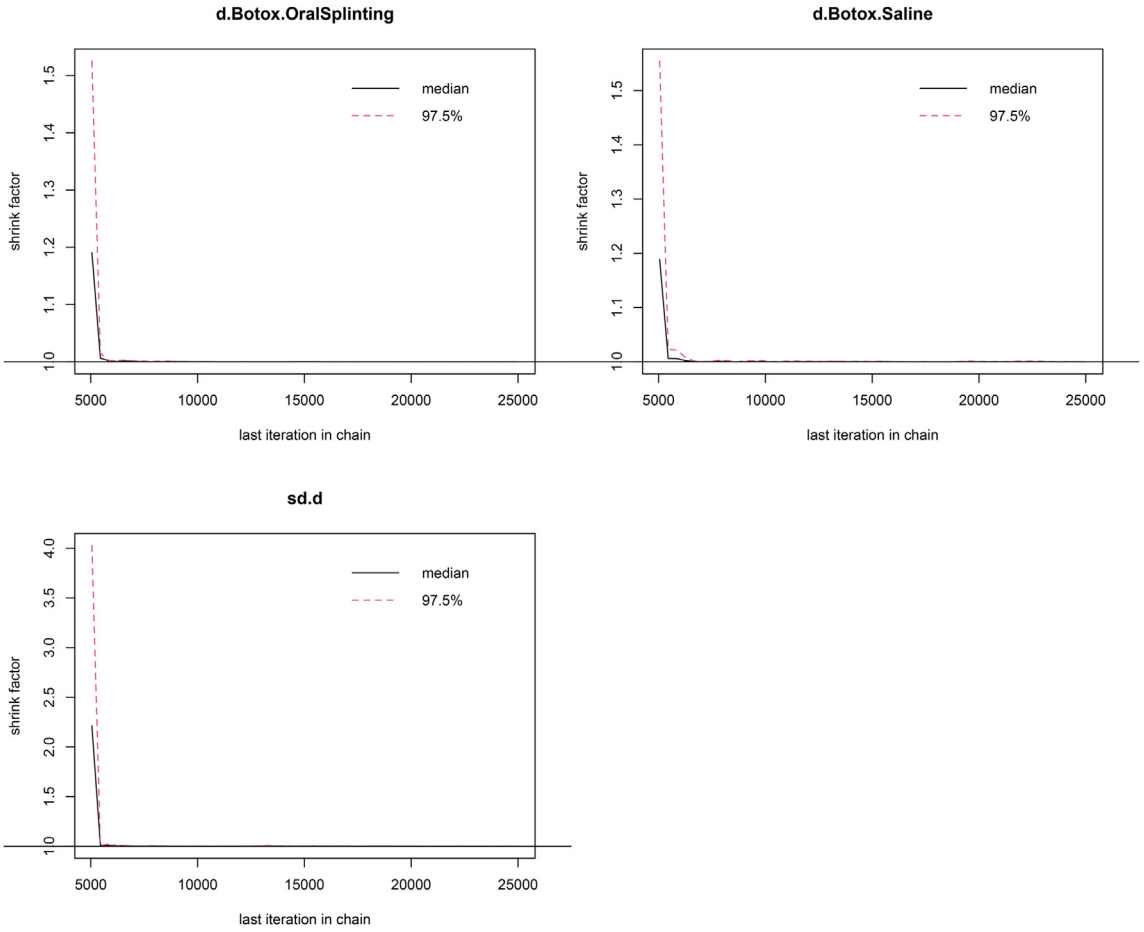

Figure 7 Convergence assessment based on Gelman plot for each outcome. BTA: botulinum toxic A; SD, satisfaction degree.

a 5-point scale to record the pain scores, the small number of options may have compromised the ability of the scale to reflect patients' pain relief accurately.

As far as we know, this is the first and largest study using single-arm meta-analysis and Bayesian network meta-analysis to investigate the efficacy of BTA in relieving bruxism-related pain. However, there are a few limitations that inevitably should be considered. First, the limited sample size in the Bayesian network meta-analysis could cause insufficient power to obtain some real statistically significant differences between BTA and oral splinting.[35] Second, this study failed to evaluate therapeutic efficacy

on bruxism by comparing BTA with other new treatments, such as clonidine, amitriptyline and clonazepam. New studies should be designed in which controls other than a mere saline injection or placebo group are compared with BTA injection, because only in this way can the value of BTA be fully reflected. Third, the included studies were not all RCTs; non-RCTs can have associated biases, such as selection bias. Finally, the most controversial issue regarding the treatment of bruxism with BTA is whether it can reduce the frequency of tooth grinding, as the injections act locally and do not affect the central nervous system. However, previous studies have suggested that BTA can markedly reduce the frequency of bruxism events, as it can limit the activity of the nerve endings responsible for bruxism.[6,36] This topic will be worth exploring in the future. Therefore, RCTs with larger sample sizes using BTA for bruxism patients and performing comparisons among BTA and other therapies are warranted.

In conclusion, within the above-mentioned limitations, BTA is effective for relieving pain caused by bruxism and more effective than oral splinting. Nevertheless, more long-term follow-up randomized controlled trials comparing BTA with other different managements or drugs are warranted.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grants from the National Nature Science Foundation of China (81671006, 81300894), CAMS Innovation Fund for Medical Sciences (2019-I2M-5—038).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2023.08.001.

References

1. De la Torre Canales G, Câmara-Souza MB, do Amaral CF, Garcia RC, Manfredini D. Is there enough evidence to use botulinum toxin injections for bruxism management? a systematic literature review. *Clin Oral Invest* 2017;21:727—34.
2. Manfredini D, Lobbezoo F. Relationship between bruxism and temporomandibular disorders: a systematic review of literature from 1998 to 2008. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;109:e26—50.
3. Lavigne GJ, Khoury S, Abe S, Yamaguchi T, Raphael K. Bruxism physiology and pathology: an overview for clinicians. *J Oral Rehabil* 2008;35:476—94.
4. Manfredini D, Cantini E, Romagnoli M, Bosco M. Prevalence of bruxism in patients with different research diagnostic criteria for temporomandibular disorders diagnoses. *Cranio* 2003;21:279—85.
5. Glaros AG, Williams K, Lausten L. The role of parafunctions, emotions and stress in predicting facial pain. *J Am Dent Assoc* 2005;136:451—8.
6. Cheng Y, Yuan L, Ma L, Pang F, Qu X, Zhang A. Efficacy of botulinum-a for nocturnal bruxism pain and the occurrence of bruxism events: a meta-analysis and systematic review. *Br J Oral Maxillofac Surg* 2022;60:174—82.
7. Huang GJ, LeResche L, Critchlow CW, Martin MD, Drangsholt MT. Risk factors for diagnostic subgroups of painful temporomandibular disorders. *J Dent Res* 2002;81:284—8.
8. Manfredini D, Winocur E, Guarda-Nardini L, Paesani D, Lobbezoo F. Epidemiology of bruxism in adults: a systematic review of the literature. *J Orofac Pain* 2013;27:99—110.
9. Murali RV, Rangarajan P, Mounissamy A. Bruxism: conceptual discussion and review. *J Pharm BioAllied Sci* 2015;7:265—70.
10. Manfredini D, Ahlberg J, Winocur E, Lobbezoo F. Management of sleep bruxism in adults: a qualitative systematic literature review. *J Oral Rehabil* 2015;42:862—74.
11. Kang MG, Park YJ, Huh KH, Kho HS. Clinical characteristics of temporomandibular disorders presenting posterior open bite - a report of 12 cases. *J Dent Sci* 2021;16:861—7.
12. Huynh N, Lavigne GJ, Lanfranchi PA, Montplaisir JY, de Champlain J. The effect of 2 sympatholytic medications-propranolol and clonidine-on sleep bruxism: experimental randomized controlled studies. *Sleep* 2006;29:307—16.
13. Mohamed SE, Christensen LV, Penchas J. A randomized double-blind clinical trial of the effect of amitriptyline on nocturnal masseteric motor activity. *Cranio* 1997;15:326—32.
14. Manfredini D, Ahlberg J, Castroflorio T, Poggio CE, Guarda-Nardini L, Lobbezoo F. Diagnostic accuracy of portable instrumental devices to measure sleep bruxism: a systematic literature review of polysomnographic studies. *J Oral Rehabil* 2014;41:836—42.
15. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980;87:1044—9.
16. Mahajan ST, Brubaker L. Botulinum toxin: from life-threatening disease to novel medical therapy. *Am J Obstet Gynecol* 2007;196:7—15.
17. Zhang A, Liu Y, Liu X, Cai X, Sun L, Li T. Could the socket shield technique be better than conventional immediate implantation? A meta-analysis. *Clin Oral Investig* 2022;26:1173—82.
18. Chen Y, Tsai CH, Bae TH, et al. Effectiveness of botulinum toxin injection on bruxism: a systematic review and meta-analysis of randomized controlled trials. *Aesthetic Plast Surg* 2023;47:775—90.
19. Roever L, Biondi-Zoccai G. Network meta-analysis to synthesize evidence for decision making in cardiovascular research. *Arq Bras Cardiol* 2016;106:333—7.
20. Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42:332—45.
21. Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. *Cranio* 2008;26:126—35.
22. Al-Wayli H. Treatment of chronic pain associated with nocturnal bruxism with botulinum toxin: a prospective and randomized clinical study. *J Clin Exp Dent* 2017;9:112—7.
23. Asutay F, Atalay Y, Asutay H, Acar AH. The Evaluation of the clinical effects of botulinum toxin on nocturnal bruxism. *Pain Res Manag* 2017;2017:6264146.
24. Jadhao VA, Lokhande N, Habbu SG, Sewane S, Dongare S, Goyal N. Efficacy of botulinum toxin in treating myofascial pain and occlusal force characteristics of masticatory muscles in bruxism. *Indian J Dent Res* 2017;28:493—7.

25. Ondo WG, Simmons JH, Shahid MH, Hashem V, Hunter C, Jankovic J. Onabotulinum toxin-s injections for sleep bruxism: s double-blind, placebo-controlled study. *Neurology* 2018;90: 559—64.
26. Yurttutan ME, Tütüncüler Sancak K, Tüzüner AM. Which treatment is effective for bruxism: occlusal splints or botulinum toxin? *J Oral Maxillofac Surg* 2019;77:2431—8.
27. Hosgor H, Altindis S. Efficacy of botulinum toxin in the management of temporomandibular myofascial pain and sleep bruxism. *J Korean Assoc Oral Maxillofac Surg* 2020;46:335—40.
28. Kaya DI, Ataoglu H. Botulinum toxin treatment of temporomandibular joint pain in patients with bruxism: a prospective and randomized clinical study. *Niger J Clin Pract* 2021;24: 412—7.
29. Alwayli M, Abdulrahman BI, Rastogi S. Does botulinum toxin have any role in the management of chronic pain associated with bruxism. *Cranio* 2023 (in press).
30. Kef K. Application of botulinum toxin in patients with secondary otalgia caused by bruxism. *J Pain Res* 2021;14:1051—9.
31. da Silva Ramalho JA, Palma LF, Ramalho KM, Tedesco TK, Morimoto S. Effect of botulinum toxin a on pain, bite force, and satisfaction of patients with bruxism: a randomized single-blind clinical trial comparing two protocols. *Saudi Dent J* 2023; 35:53—60.
32. Lee WH, Shin TJ, Kim HJ, et al. Intrathecal administration of botulinum neurotoxin type a attenuates formalin-induced nociceptive responses in mice. *Anesth Analg* 2011;112: 228—35.
33. Freund B, Schwartz M. The use of botulinum toxin for the treatment of temporomandibular disorder. *Oral Health* 1998; 88:32—7.
34. Lee SJ, McCall Jr WD, Kim YK, Chung SC, Chung JW. Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial. *Am J Phys Med Rehabil* 2010;89: 16—23.
35. Shitsuka C, Palma LF, Pedron IG, et al. Salivary profile of children with erosive tooth wear: a transversal study. *Braz Oral Res* 2020;34:e115.
36. Shim YJ, Lee MK, Kato T, Park HU, Heo K, Kim ST. Effects of botulinum toxin on jaw motor events during sleep in sleep bruxism patients: a polysomnographic evaluation. *J Clin Sleep Med* 2014;10:291—8.