Systematic Review
Pediatric Dentistry

Efficacy of treatments used to relieve signs and symptoms associated with teething: a systematic review

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Abstract: The purpose of this review was to systematically evaluate all the existing literature on the efficacy of treatments used to relieve the signs and symptoms associated with teething. A systematic search up to February 2021, without restrictions on language or date of publication, was carried out in MEDLINE/PubMed, SCOPUS, Web of Science, The Cochrane Library, EMBASE, LILACS, BBO, OpenGrey, Google Scholar, Portal de Periódicos da CAPES, clinicaltrials.gov, and the references of the included studies. Clinical studies that evaluated the effect of any intervention to alleviate the signs and symptoms associated with teething in babies and children were included. The risk of bias was assessed using the ROB-2 and ROBINS-I tools. The characteristics and results of the individual studies were extracted and synthesized narratively. The GRADE approach was followed to rate the certainty of the evidence. Three randomized and two non-randomized clinical trials were included. The outcomes of these five articles were classified as high or serious risk of bias. Three studies using homeopathy reported improvement in appetite disorders, gum discomfort, and excess salivation. One study showed a new gel with hyaluronic acid was more effective than an anesthetic gel in improving signs and symptoms such as pain, gingival redness, and poor sleep quality. Another study applied non-pharmacological treatments, which were more effective, especially against excess salivation. Although the present systematic review suggests some therapies could have a favorable effect on signs and symptoms related to teething, definitive conclusions on their efficacy cannot be drawn because of the very low certainty of the evidence. The existing literature on the subject is scarce and heterogeneous and has methodological flaws; therefore, further high-quality investigations are necessary.

Keywords: Tooth Eruption; Therapeutics; Signs and Symptoms; Clinical Trial; Systematic Review

Introduction

Tooth eruption is the physiological process of movement of teeth from inside the jaw to their position in functional occlusion in the oral cavity.[1] This process starts on average at 6 months of age and can cause local inflammatory symptoms, as well as signs and symptoms in the general health of babies and children.[2]

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Although no consensus exists in the literature on the direct association between local and health signs and symptoms with the tooth eruption phase, some authors believe in this relationship.[3,4] The main signs and symptoms reported by parents and guardians include fever, diarrhea, finger sucking, irritability, excess salivation, and poor appetite.[3,5,6] This process can cause significant discomfort in babies and children and worry and anxiety in parents.[7].

Appropriate and effective treatment methods and clinical studies to evaluate them are scarce in the literature. Therefore, given that pediatric dentists have no consensus on the best and safest treatments, several treatments are the choice of parents themselves.[8] Pharmacological or non-pharmacological treatments may be prescribed during this process, but no evidence has been gathered about their efficacy.

Non-pharmacological methods, including homeopathy and calming teas such as chamomile used for local massages, are the first-choice treatments used by parents because they are considered safer and less likely to cause side effects.[9] Although pharmacological treatments can also be chosen to treat the signs and symptoms of tooth eruption, their use can be considered risky because medications such as analgesics or local anesthetics carry a high risk of toxicity when administered indiscriminately by parents.[10]

Because no prior systematic review exists on this subject, and controversies remain about the best treatments to be used during the tooth eruption phase, creating uncertainty of health professionals over their prescription, the objective of this review was to systematically evaluate all existing literature to answer the following focused question: what is the efficacy (O) of the treatments used to alleviate the signs and symptoms associated with teething (I/C) in babies and children (P)?

Methodology

The present systematic review was reported in accordance with the PRISMA 2020 statement.[11]

Eligibility criteria

Eligibility was defined following the PICO framework, as follows:

a. Participants: Studies assessing babies and/or children of both sexes and all ethnicities with one or more symptoms associated with teething during the eruption of primary teeth were included. Studies evaluating children who had already used some treatment to relieve signs and symptoms, with serious concomitant diseases such as cardiac anomalies, circulatory failure, cardiomyopathy, decompensated kidney and liver, immunosuppressive conditions, cancer, known or suspected hypersensitivity to any drug or therapy, hyperthermia over 38.0°C, among other conditions influencing their health status were excluded.
b. Intervention/comparison: any treatment to alleviate signs and symptoms associated with teething. Because there is no reference treatment for the condition studied, we decided to be as comprehensive as possible in the establishment of eligibility criteria and consequent selection; therefore, we planned to include any of the following possibilities: experimental intervention vs. untreated control, experimental intervention vs. placebo, experimental intervention vs. experimental intervention, or even before and after uncontrolled studies (in this case, we would simply evaluate treatment changes rather than the efficacy).
c. Outcomes: Relief of signs and symptoms associated with teething such as diarrhea, green stools, yellow stools, stool softening, constipation, vomiting, drooling, irritability, pain, red and itchy gums, anxiety, fever, loss of sleep, sleep-wake disorders, chewing objects, runny nose, pain, swelling of the gums, earache, cough, crying, colic, loss of appetite, and spasms in the mouth. Outcomes reported in any follow-up period would be assessed.

Interventional studies (randomized and non-randomized clinical trials, as well as single-parallel studies with before-and-after comparisons) would be eligible. Despite the initial plan to include observational studies, after conducting preliminary searches, we decided to restrict the review to interventional studies only. Literature reviews, case reports, experts' opinions, and letters to the editor were excluded.

Information sources, search strategy, and selection process

Electronic searches were performed in the following databases: MEDLINE (PubMed), SCOPUS (Elsevier), Web of Science Core Collection (Web of Science), The Cochrane Library (Wiley), EMBASE (Elsevier), LILACS (Virtual Health Library), and BBO (Virtual Health Library). Grey literature was consulted through OpenGrey, Google Scholar (first 100 records), and the Portal de Periódicos da CAPES. The Clinicaltrials.gov registry was also scrutinized to identify possible ongoing or completed studies that have not yet been published. Additionally, manual searches of the reference lists of the included studies were performed, and experts in the field were contacted to identify ongoing studies or unpublished research. The search procedures were initially conducted in June 2020, and alerts were created in databases to keep the search updated until the date of the manuscript submission (February 2021).

The search strategy was first developed for MEDLINE (PubMed) using Mesh terms, synonyms, and free terms, and then adapted for the other databases and grey literature sources following the syntax rules of each (Supplementary Material 1, available at https://osf.io/64uvf/). For the searches in the Virtual Health Library platform, the strategies included synonyms in Portuguese for each of the terms included. No restrictions were applied to the language or date of publication of the articles. All search procedures were supervised by an experienced librarian (DMTPF).

All the articles identified were imported into Online EndNote®, version X7 (Clarivate Analytics), and duplicates were removed automatically and manually. Three review members (FMTC, OCCN, and JML) independently carried out the study selection, identifying the eligible studies by initially reading the titles and abstracts. In case of disagreement during the selection process, a consensus meeting was held. The eligible articles were then read in full for a final selection by the same three authors. Again, a consensus meeting among the review members was held, with the participation of a fourth reviewer (LCM) in case of disagreements, for the final decision. When the full texts of the selected articles could not be obtained, attempts were made to contact the authors by email or social networks weekly for five consecutive weeks.

Data collection process and data items

The data were extracted from the selected articles by three independent review members (FMTC, OCCN, and JML). A consensus meeting was held to check the extracted data, and any disagreement was resolved with a fourth author (GMV). The article data were extracted into an Excel spreadsheet (Excel®, Microsoft®, USA) and organized into the following topics: authors, year, and country of publication; study design; sample size and age; treatment strategies applied; therapy details; outcomes assessed; outcome evaluation methods; evaluation periods; and results and main conclusion of the study. In case of missing data, the authors were contacted following the approach described in the previous section. If any article was in a language other than English, the Google Translate app tool was used to translate it.

Study risk of bias assessment

The risk of bias assessment for the included studies was carried out independently by two review authors (FMTC and JML). After a consensus meeting, a third review author (GMV) intervened in case of disagreements for the final decision.

Two different tools (ROB-2 and ROBINS-I)[12,13] were used for the risk of bias assessment. The ROB-2 tool was used to assess the risk of bias in the findings of randomized controlled trials.[12] This instrument assesses five domains of risk of bias related to the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcomes, and the selection of the reported result. Signaling questions are answered with "yes," "probably yes," "no," "probably no," or "no information." Based on these answers, a risk of bias judgment ("low" or "high" risk of bias or "some concerns" related to the risk of bias) is issued for each domain, and then an overall risk of bias judgment is determined.

The ROBINS-I tool was used to assess the risk of bias in the non-randomized studies. This instrument assesses seven domains on the risk

of bias related to confounding, selection of the participants, misclassification of the interventions, deviations from the intended interventions, missing outcome data, measurement of the outcomes, and selection of the reported results. Similar to the ROB-2 tool, signaling questions can be answered with "yes," "probably yes," "no," "probably no," or "no information." Based on these answers, a risk of bias judgment ("low," "moderate," "serious," or "critical" risk of bias or "no information") is issued for each domain, and then an overall risk of bias judgment is determined.

When sufficient data were missing for the judgment of any study, the authors were contacted following the approach described in previous sections.

Synthesis methods and certainty of evidence assessment

Narrative syntheses would be conducted for the results reported on each outcome and for each specific comparison between interventions. As pre-established in the protocol, a quantitative synthesis was planned depending on the clinical and methodological heterogeneity of the included studies.

Random effects meta-analyses would be performed to estimate mean differences or standardized mean differences for the outcomes reported as continuous data, or the relative risk of presenting a certain outcome reported as categorical data, between the intervention and comparator groups (or between pre- and post-treatment evaluations in uncontrolled before-and-after studies). Additionally, publication bias would be evaluated for quantitative syntheses including more than 10 datasets.

The certainty of evidence was determined using the Grading of Recommendations, Assessment, Development and Evaluation Pro software (GRADEpro Guideline Development Tool).[14-16]

Results

Study selection

A total of 4,747 records were identified by the searches in the databases. After duplicate removal, 3,040 records were screened by reading the titles and abstracts. From a total of 22 initially selected articles, two full texts were not retrieved despite attempts to contact the authors.[17] Twenty articles were assessed for eligibility, and 15 were excluded (reasons are shown in Figure 1 and available at Canto et al.[17] An additional 160 documents were identified via other methods, but none were eligible after reading the titles and abstracts. Finally, five articles[9,18-21] were selected, all from databases. The study selection process is presented in Figure 1.

Study characteristics

The five selected studies[9,18-21] were carried out in different countries: Iran, India, Holland, Romania, and Russia. The studies[9,18-21] were published between 2015 and 2018. Three[19-21] were randomized and two[9,20] were non-randomized controlled studies. The age of the participants in the studies[9,18-21] ranged from 6 to 36 months.

No standard type of treatment was used equally in all studies. Each used a type of treatment method, including non-pharmacological methods, hyaluronic gel, and homeopathy, to relieve the signs and symptoms of tooth eruption. Only one study[9] chose to use five types of non-pharmacological methods and compare them; three studies[19-21] used homeopathy as treatment, and one[20] used a new treatment with a gel containing hyaluronic acid.

In the five studies,[9,18-21] the outcome was the improvement of symptoms caused by the tooth eruption process, such as drooling, diarrhea, fever, loss of appetite, lack of sleep, gum irritation, chewing objects, finger sucking, irritability, red and inflamed gums, gingival pain, mouth spasm, poor sleep quality, and unmotivated anxiety. The only common outcomes in the five articles[9,18-21] were irritability and some gingival discomfort. The data were obtained through the application of a questionnaire for three studies[9,20,21] and interviews for two studies.[18,19] The monitoring of the studies[9,18-21] ranged from 3 days to 1 month. The characteristics of each selected article[9,18-21] are shown in Table.

Risk of bias in the studies

Of the five selected articles,[9,18-21] three[18-20] were assessed for risk of bias with the ROB-2 tool[12] (Figure 2) and classified as having a high risk of bias. When

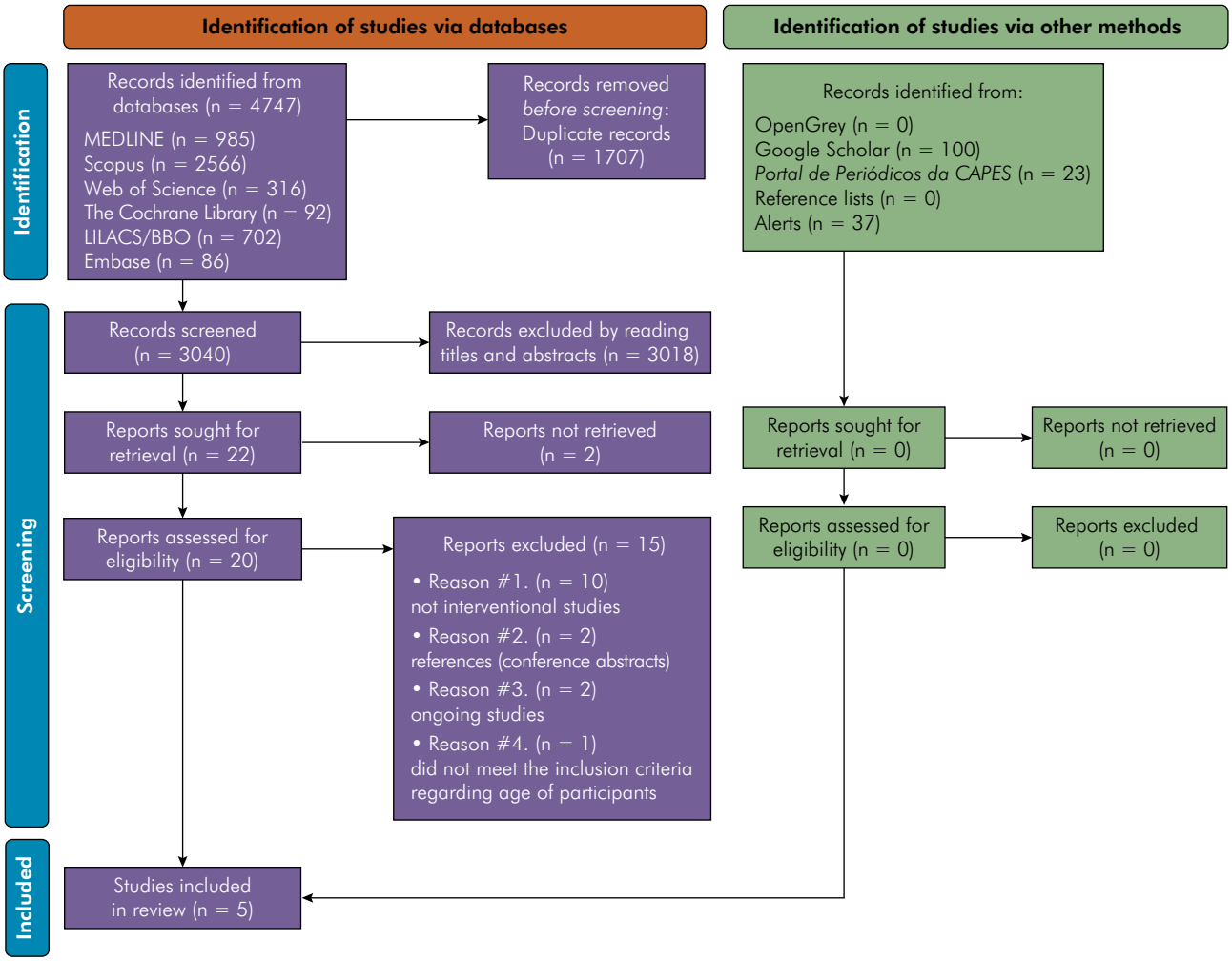

Figure 1. Flow diagram of the literature search

assessing the domain of randomization process, only the study by Jong et al.[20] was classified as having a low risk of bias. It described all the information in the randomization process as the random component used in the sequence generation process, as well as the blinding of randomization using brown envelopes, revealing the group of each participant only at the moment of the intervention. The other two studies had some concerns. When evaluating the domains of deviations from the intended interventions (effect of adhering to intervention), three studies[19-21] were classified as having some concerns. In missing outcome data, three studies[19-21] were classified as low risk of bias for these domains. The measurement of the outcome domain was evaluated for the measurement of fever and subjective signs and symptoms that depended on parental reporting. When related to the measurement of fever, the studies by Rosu et al.[19] and Kazyukova et al.[21] were classified as having some concerns. For the same domain, the same studies were classified as high risk when related to subjective signs and symptoms reported by parents. In the last domain, two studies contained the registered protocol and were classified as low risk (there was no apparent selection in the report), and one did not have this information and was classified as having some concerns.

Two non-randomized studies[9,18] were evaluated using the ROBINS-I tool (Figure 3) and classified overall as having a serious risk of bias. The study by Mermapour et al.[9] had five domains classified as low risk of bias and two domains classified as serious risk

Table. Characteristics of the included studies.

Author, Year, Country	Study design	Total sample size	Sample age	Treatment strategies		Outcomes-related information			Results	Conclusion	Funding source	Conflict of interest report
				Group(s) / Interventions assessed	Therapy details	Outcomes assessed	Assessment methods	Evaluation periods				
Taneja et al., 2018, India	Non randomized clinical trial	n = 11426	6 to 12 months	Calcarea phosphoricum 6x	Tablet twice a day regularly for 12 months (6 to 12 months)	Fever, colic, running nose, irritability, crankiness, crankiness, restlessness, no sleep, refusal to eat food, green stools, diarrhea, yellow stool.	visited the household frequently by ASHAs (Accredited Social Health Activists) or were in contact with the parents by telephone or through a messenger to confirm health of the telephone or through a messenger to confirm health of the child.	month to month	ASHAs (n = 566) who had provided care to children gave their feedback:CP. 6X-330 ASHAs responded that CP helped in easy teething 41 ASHAs : it reduced complaints associated with teething 195 responded CP eased teething as well as reduced associated complaints. 515/581 ASHAs responded:the six medicines IMPROVE: (Symptoms of teething such as increased salivation, irritability, and gum swelling 307/581 ASHAs responded: six medicines IMPROVE : (Diarrhea) 11/581 ASHAs responded:the six medicines NO EFFECT	Children responded favorably to the medicines given by ASHAs at the time of diarrhea/URTI episodes, and ASHAs expressed satisfaction with the program.	Central Council for Research in Homoeopathy, an autonomous body of the Ministry of AYUSH, Government of India.	None declared
				Ferrum phosphoricum 3X,	2 tablets 4x/day for maximum 3 days (Child with fever)							
				Magnesium phosphoricum (mp) 6x	2 tablets dissolved in hot water for 1 to maximum 2 days (child with colic)							

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Taneja et al., 2018, India	Non randomized clinical trial	n = 11426	6 to 12 months	Belladonna 30C	3 pills 4x/day for maximum 3 days (Child with running nose, fever)		month to month	Children responded favorably to the medicines given by ASHAs at the time of diarrhea/URTI episodes, and ASHAs expressed satisfaction with the program.			
				Chamomilla 30C	3 pills 4x/day for maximum 3 days (Child with irritability, crankiness, restlessness, no sleep, refusal to eat food, green stools)						
				Podophyllum 30c	3 pills 4x/day for maximum 3 days. (Child with diarrhea, yellow, offensive stool)						
Jong et al., 2015, The Netherlands	Randomized Open Comparative Clinical Trial	n = 200	Infants < 12 months	ChamBell 5: 02 tablets (Dentokind®; intervention group)	ChamBell 5: 02 tablets containing: Belladonna D6, Chamomilla D6, Ferrum	Unmotivated anxiety, gingival tenderness and appetite disorder, otalgy, stool softening, sleep-onset insomnia and frequent awakenings kin pallor, gingiva condition: hyperemia, swelling, hematoma and hyperemia around the mouth, drooling and hyperthermia.	interview	0 7 days	Individual signs improved after seven days of treatment: intervention(n=100) /control group(n=100):unmotivated anxiety (88%/79%), gingival tenderness (73%/55%) (p=0.0130), appetite disorder (83%/66%) (p=0.0107), otalgy(56%/18%), stool softening (75%/36%), sleep-onset insomnia(57%/54%) and frequent awakenings (74%/59%), skin pallor (33%/30%), gingival hyperemia (91%/ 75%) (p = 0,0057); gingival swelling (59%/41%) (p = 0,0157); drooling (86%/83%), hyperemia around the mouth (51%/37%), hyperthermia(82%/86%).	ChamBell 5: 02 tablets showed to be effective, safe and well tolerated.	Deutsche Homöopathie-Union, DHU-Arzneimittel GmbH & Co. KG, Karlsruhe, Germany .	M. Jong was an employee of VSM Geneesmiddelen (sister company of Deutsche Homöopathie Union) from 2001 to 2008 P. Klement and J. Burkart are employees of Deutsche Homöopathie Union, DHU Arzneimittel GmbH & Co. KG, Karlsruhe, Germany.)

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Jong et al., 2015, The Netherlands	Randomized Open Comparative Clinical Trial	n = 200	Infants < 12 months	ChamBell 5: 02 tablets (Dentokind®; intervention group)	phosphoricum D6, Hepar sulfuris D12 and Pulsatilla D6 (for seven days). six tablets per day (acute symptoms). After symptoms reduced one tablet three times a day was administered	interview	ChamBell 5: 02 tablets showed to be effective, safe and well tolerated.
				homeopathic suppositories (Viburcol®; control group).	Chamomilla recutita D1, Atropa bella donna D2, Solanum dulcamara D4, Plantago major D3, Pulsatilla pratensis D2, Calcium carbonicum Hahnemanni D8.(seven days). For children aged up to six months: two suppositories a day. Children older than six months: four suppositories.)	(ChamBell-5-02 tablets showed to be effective)	

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	Randomized, open-label, parallel-group (multicentre study)						Questionnaire and clinical examination Verbal Rating Scale: (VRS)Absent = 0; Moderate = 1; Intense = 2.	baseline (T0), three days (T1)	Pain			
								seven days (T2)	T0 : test: 1.59 (0.50)/ control:1.44 (0.51) p=0.2849			
								14 days	T1:test: 1.18 (0.62)/ control:1.7 (0.47) p=0.0018			
								(T3)	T2:test:0.10 (0.33)/ control:0.86 (0.73) p<0.0001 Swelling: T0: test:1.70 (0.47)/control: 1.56 (0.51) p=0.2686 T1:test: 1.44 (0.51)/control:1.63 (0.49) p=0.1796 T2:test: 0.39 (0.57)/control:0.91 (0.71) p=0.0087 Redness: T0: test:1.63 (0.56)/control: 1.63 (0.49) p=0.8678 T1:test:1.19 (0.56) /control:1.70 (0.47) p=0.0009 T2:test: 0.13 (0.40)/control:1.01 (0.63) p<0.0001 mouth spasm:T0 – T1 (p=0.1648); T0 – T2 (p=0.1184);T2-T3 (p=0.3363). Sleep quality was better in the test group than in the control group at T1 (p=0.0171) and T2 (p=0.0016			
Rosu et al., 2017, Romania		n = 54	3 to 36 months	Group A: high molecular weight hyaluronic acid (HMWHA) gel :0.54% Hyaluronic Acid; (test group)	Group A: massaging the surface around the teeth and applying locally a small amount of gel, up to a maximum of 6 times per day.	Pain, swelling and redness, mouth spasm, sleep quality.				The novel gel containing HMWHA proved to be an effective and safe alternativeto the anesthetic gel in the relief of teething symptoms in infants.	Ricerfarma S.r.l. (www.ricerfarma.com)	Have no financial interest

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				Group B: standard anesthetic gel: cetylpyridinium chloride and lidocaine hydrochloride (control group)	Group B: massaging the surface around the teeth and applying locally a small amount of gel, up to a maximum 4 times per day.							
Kazyukova et al., 2018, Russia	Randomized clinical trial	n = 63	6 months to 2,5 years	Principal Group: Dantinorm Baby (Homeopathy -liquid)	Principal Group: Dantinorm Baby :2/3 to 5 times(maximum) / 3 days (maximum, no more than 5 days). dripping content into the child's mouth (1 dose = 1 ml). The main components: chamomile (chamomilla vulgaris) reduces tantrum and body temperature; (phytolacca decandra) reduces nausea and inflamed gums; (rheum officinale) relieves digestion symptoms	Pain and swelling of the gums Increased salivation	Visits and parent's report	Visit 1: initial inspection Visit 2: 3rd to 5th day	teething symptoms and their severity in the groups compared with initial examination before study therapy (visit 1) Dantinorm Baby : (%) (n=31) Pain and swelling of the gums(100%) / Increased salivation(100%)/ Wish to bite / bite(100%)/ Irritability (96,8%)/Decreased appetite (77,4%)/Sound disorders (74,2%); Increased body temperature> 37 0 □ (61,3%)/Running nose (48,4%); Cough (48,4%)/ Irritation of the skin around the mouth (35,5%);Increased stool (25,8%).	«Dantinorm Baby» drug, which is designed on the basis of plant substances, in a liquid dosage form. It has no contraindications, does not cause side effects, does not increase the pharmacological load on the growing organism, and can be recommended for wide use in pediatric practice.	None declared	Have no financial interest

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Kazyukova et al., 2018, Russia	Randomized clinical trial	n = 63	6 months to 2,5 years	Principal Group: Dantinorm Baby (Homeopathy -liquid)	Wish to bite / bite Irritability Decreased appetite Sound disorders Increased body temperature Running nose Cough Irritation of the skin around the mouth Increase sed stool	Visits and parent's report	Calgel : (%) (n=32) Pain and swelling of the gums(100%)/ Increased salivation(100%)/ Wish to bite / bite(100%)/ Irritability (100%)/ Decreased appetite (81,3%)/Sound disorders (65,6%)/Increased body temperature> 37 0 □ (62,5%)/ Running nose (40,6%)/Cough (40,6%)/ Irritation of the skin around the mouth (37,5%)/ Increased stool (28,1%) teething symptoms and their severity in the groups compared with initial examination before study therapy (visit 2): Pain and swelling of the gums(90,3%) /Increased salivation(90,3%)/ Wish to bite / bite(87,1%)/Irritability (58,1%)/Decreased appetite (35,5%)/Sound disorders (32,3%) -Increased body temperature> 37 0 □ (35,5%)/Running nose (35,5%) Adverse events: G control: 6/32	«Dantinorm Baby» drug, which is designed on the basis of plant substances, in a liquid dosage form. It has no contraindications, does not cause side effects, does not increase the pharmacological load on the growing organism, and can be recommended for wide use in pediatric practice.	None declared	Have no financial interest

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				Control Group: Calgel	Control Group: Calgel applying the gel with your finger, gently massaging the inflamed gum; if necessary, reapply at intervals of at least 20min, but no more than 6 times / day, for 3 days. The main components: lidocaine hydrochloride and cetylpyridinium chloride					«Dantinorm Baby» drug, which is designed on the basis of plant substances, in a liquid dosage form. It has no contraindications, does not cause side effects, does not increase the pharmacological load on the growing organism, and can be recommended for wide use in pediatric practice.		
Memarpour et al. / 2015 / Iran	Non randomized clinical trial	n = 254	8 to 36 months	Cuddle therapy (n=53)	Hug or cuddle the child. Activities to distract the child.	Drooling, Diarrhea, lethargy, Loss of appetite, Lack of sleep, Gum irritation, chewing objects, Finger sucking, Irritability, Red and inflamed gums, Gingival pain, Crying.	Questionnaire contained 27 items. Body temperature was measured; Body temperature was measured; and Intraoral examination (palpation).	4 days before eruption, On the day of eruption and 3 days after eruption.	Cuddle therapy (frequency of successful cases) Drooling (n=47), Lethargy (n=13), Loss of appetite (n= 21); Lack of sleep (n=41); Gum irritation (n=36); Chewing objects (n= 29); Finger sucking (n=26); Irritability(n=6); Red and inflamed gum(n=11); Gingival pain (n= 18); Crying (n=41). Pieces of ice (frequency of successful cases)	Teething rings, cuddle therapy and rubbing the gums were the most effective methods to reduce symptoms.	Vice Chancellory of Research of Shiraz University of Medical Science, Shiraz, Iran.	No competing interests.
				Pieces of ice (n=50)	Pieces of ice wrapped in a towel were placed on the gums and mucous membrane overlying the erupting teeth for 1 to 2 min.							

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							Drooling (n=29); Lethargy (n=17); Loss of appetite (n=22); Lack of sleep (n=41); Gum irritation (n=36); Chewing objects (n= 39); Finger sucking (n=37); Irritability(n=6); Red and inflamed gum (n=29); Gengival pain(n=16); Crying (n=38). Teething rings (frequency of successful cases)		
Memarpour et al. / 2015 / Iran	Non randomized clinical trial	n = 254	8 to 36 months	Rubbing the child's gums (n=50)	Massage for 1 to 2 min.	Drooling, Diarrhea, lethargy, Loss of appetite, Lack of sleep, Gum irritation, chewing objects, Finger sucking, Irritability, Red and inflamed gums, Gingival pain, Crying.	Drooling (n=47); Lethargy(n=11); Loss of appetite (n=17); Lack of sleep (n=40); Gum irritation (n=29); Chewing objects (n= 33); Finger sucking (n=40); Irritability (n=16); Red and inflamed gum(n=21); Gingival pain (n= 18); Crying (n=34). Food for chewing (frequency of successful cases)	Teething rings, cuddle therapy and rubbing the gums were the most effective methods to reduce symptoms.	
				Teething rings (n=51)	Give the ring to the child to chew or bite on.		Drooling (n= 37); Lethargy (n=9); Loss of appetite (n= 31); Lack of sleep(n=32); Gum irritation (n=29); Finger sucking (n=23); Chewing objects(n=21); Irritability(n=16); Red and inflamed gum(n=15); Gengival pain(n=14); Crying (n=32).		
				Food for chewing (n=50)	Pieces of a frozen fruit or vegetable.				

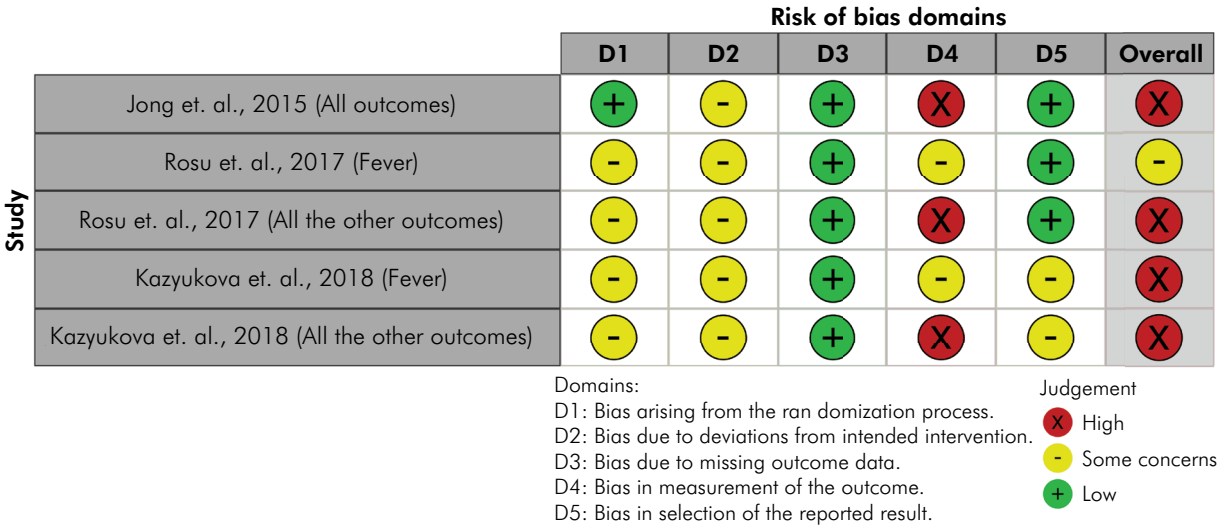

Figure 2. Quality assessment of included studies according to ROB-2 tool.

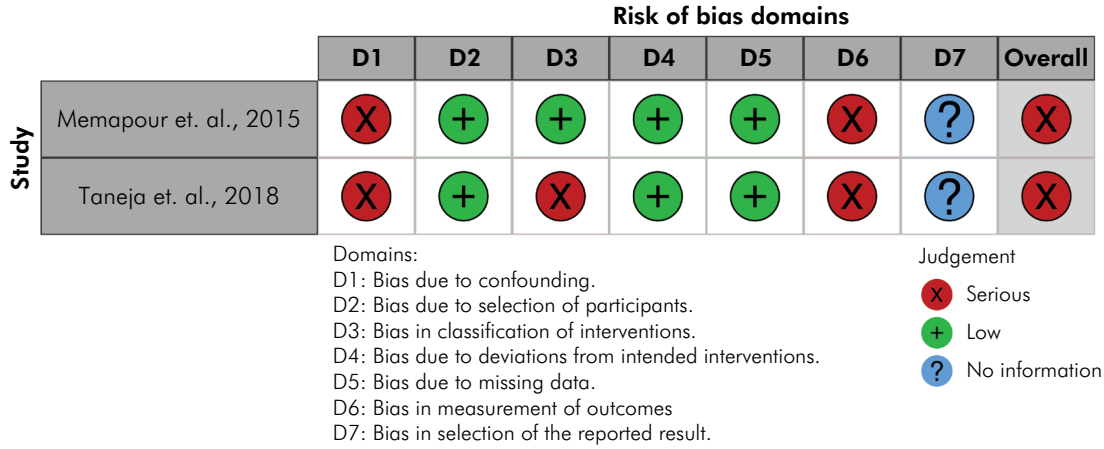

Figure 3. Quality assessment of included studies according to ROBINS-I tool.

of bias due to flaws in the control of confusion bias and participants' knowledge about the treatments studied, qualifying this study in general as having a serious risk of bias. The study by Taneja et al.[18] had four domains classified as serious risk of bias due to flaws in the control of confusion bias, knowledge of the participants about the treatments studied, failures in the selection of study participants (the beginning of the intervention not coinciding with monitoring), and failures in the classification of interventions; it had three domains classified as low risk of bias. Detailed assessments of risk of bias are presented in Canto et al.[17]

Results of individual studies and syntheses

The results of each outcome of the individual studies are shown in Table 1. All studies evaluated alternative practices used to relieve the signs and symptoms of tooth eruption. Among them, homeopathy was the most prevalent. Of the five studies[9,18-21] included, three[18,20,21] evaluated homeopathic therapies. Although the evaluated therapies were different, they all showed a favorable effect for outcomes such as appetite disorders, gum discomfort, and excess salivation. The study by Taneja et al.[18] used six types of homeopathic remedies (*calcarea phosphoricum*, *ferrum phosphoricum*, *magnesium phosphoricum*, belladonna,

chamomile, and podophyllum) that were effective in improving the signs and symptoms evaluated, such as increased salivation, irritability, gum swelling, and diarrhea. Of 581 ASHAs, 515 responded that the six remedies applied to children improved teething symptoms such as increased salivation, irritability, and gingival swelling, and 307 responded that they improved diarrhea.

The study by Jong et al.[20] also used homeopathic treatments, comparing two groups. One used tablets (belladonna D6, chamomilla D6, *ferrum phosphoricum* D6, *hepar sulfuris* D12, and pulsatilla D6), and the other used a suppository (*chamomilla recutita* D1, *atropa belladonna* D2, *solanum dulcamara* D4, *plantago major* D3, *pulsatilla pratensis* D2, and *calcium carbonicum hahnemanni* D8). The study showed better results for signs and symptoms with oral treatment, mainly related to gingival tenderness (73%), appetite disorder (83%), and gingival hyperemia (91%) when compared to the control group.

The study of Kazyukova et al.[21] compared a homeopathic remedy in liquid form (*chamomilla vulgaris*, *phytolacca decandra*, and *rheum officinale*) with topical lidocaine gel. The homeopathic product showed significant improvement after 5 days of use in signs and symptoms such as pain and swelling of the gums (100%), increased salivation (100%), wish to bite (100%), irritability (96.8%), decreased appetite (77.4%), and speech sound disorders (74.2%). With the use of lidocaine gel, adverse effects occurred in six of the 32 participants.

The study by Memarpour et al.[9] compared non-pharmacological treatment methods and found the most effective were teething rings, mainly related to the symptoms of drooling (n = 47/53), lack of sleep (n = 41/53), gum irritation (n = 36/53), and crying (n = 34/53).

The study by Rosu et al.[19] compared the use of a new gel based on hyaluronic acid with a gel based on 2% lidocaine. It was found that after 7 days of use, the new gel was more effective in the improvement of pain ($p = 0.0018$), redness ($p = 0.0009$), and sleep quality ($p = 0.0171$).

Due to clinical and methodological heterogeneity among the studies, as well as differences in the interventions and outcomes assessed, a meta-analysis could not be applied. The certainty of the evidence was rated as very low. Direct evidence for comparisons between specific interventions was only constituted by one study in all cases; therefore, the inconsistency item could not be evaluated. The risk of bias was considered to have affected the evidence very seriously (two-level downgrade) due to the important methodological limitations presented by the studies. In addition, for almost all comparisons, the number of subjects evaluated was insufficient, affecting the imprecision item (one-level downgrade).

Discussion

Although no consensus exists in the literature on the association of signs and symptoms with the tooth eruption process, they are undeniably present during the development phase of babies and children, and some studies have found this association.[8,22] The ideal and most effective treatment in this period in the baby's life remains unclear. For this reason, this systematic review aimed to investigate primary studies that could prove the efficacy of treatments used during the tooth eruption phase to relieve its signs and symptoms.

Interventional clinical studies were part of the eligibility criteria, as they assess the efficacy of therapies and have a higher quality rating.[23] Our review included primary studies that dealt with the symptoms of tooth eruption. From the searches carried out with specific terms for signs and symptoms, tooth eruption, and therapies, 4,747 articles were found. Only five articles[9,18-21] were included in this review based on the eligibility criteria because most of the studies found were observational, presenting a lower quality rating. This shows that there are few studies on the subject, possibly due to this lack of consensus on whether these signs and symptoms really concern the tooth eruption process and also, probably, due to the longevity and cost of clinical studies.

When assessing the risk of bias in the five eligible studies,[9,18-21] all were classified as high, and the domain of measurement of results was essential for the articles cited to obtain this classification. This is because these studies used self-report questionnaires or interviews with a parent or guardian in their study

design to measure the outcomes, generating a high risk of memory bias, given that parents may not completely remember information and symptoms presented by babies or children.

The studies eligible[9,18] for this review were not homogeneous in the treatments or outcomes studied, with no standard treatment versus the same control, thus being a limitation of this systematic review. For this reason, a meta-analysis of results was not possible. Despite this, it was possible to analyze the results of each study descriptively. The study by Memarpour et al.[9] was the only one that used non-pharmacological methods to treat signs and symptoms, obtaining better results with the use of teething rings for 3 days after the eruption. Having an effective result for this type of non-pharmacological treatment is extremely important for both parents and pediatric dentists and pediatricians. The latter need to be cautious when prescribing medications such as painkillers or anti-inflammatory drugs, because they have a high chance of causing toxicity in children, whose liver and kidney systems are still immature.[10]

Three studies[18,20,21] selected for this review used homeopathic remedies as treatment. All of them showed significant benefits in signs and symptoms of tooth eruption such as decreased appetite, speech sound disorders, increased body temperature, runny nose, cough, irritation of the skin around the mouth, unmotivated anxiety, gingival tenderness and appetite disorder, otalgia, stool softening, delayed sleep onset, insomnia, colic, and diarrhea. In addition, the studies previously mentioned used some of the same components in their medications, such as chamomile and *ferrum phosphoricum*. These two homeopathic components are beneficial because of their anti-inflammatory, antispasmodic, antithermal, and sudorific actions,[24,25] which can lead to significant improvement in the aforementioned signs and symptoms.

The study by Rosu et al.[19] compared a gel based on hyaluronic acid with 2% lidocaine gel used for topical application in cases of inflamed and painful gums. Both showed good efficacy and tolerability, with two adverse effects not related to the use of the product. However, lidocaine gel carries a high risk of toxicity, methemoglobinemia, and problems with the central nervous system in babies because they are still developing,[26] especially if the gel is administered indiscriminately and excessively to the mucosa of babies and children without supervision by the health team.

The present review has some limitations. Although the selection criteria were broad both for the types of intervention and clinical trial design, as well as for the outcomes assessed, few studies were eligible. In addition, two records could not be recovered despite our efforts. The selected reports differed from each other in terms of their methodology and reporting of the results, which made it difficult to synthesize and consequently obtain clear answers to the focused question of the review. Regardless of this heterogeneity, we can affirm that the results of the effect of the reviewed interventions on the symptoms associated with teething still have very low certainty, due to the poor methodological quality of the studies and the consequent presence of bias, as well as insufficient sample sizes. Unfortunately, although some of the identified therapies may show favorable effects, we still lack scientific support that is strong enough to recommend one of them for use in clinical practice. The signs and symptoms associated with teething are relatively common problems that affect not only babies but their family environment, for which we currently have more empirical recommendations than accurate treatment indications. This systematic review highlights the scarcity of interventional studies on the subject and demonstrates to the scientific community that there is a need for new high-quality studies. Future research should preferably include, if possible, appropriately conducted RCTs that evaluate powerful samples, in which researchers minimize the bias generated by deviations in adherence to intervention protocols and whose outcomes are evaluated more objectively.

Conclusion

The findings of the present systematic review suggest that some therapies could have a favorable effect on signs and symptoms related to teething. However, definitive conclusions on their efficacy cannot be drawn due to the very low certainty

of the evidence. Interventional primary research on the subject is scarce, heterogeneous, and has methodological flaws; therefore, more high-quality studies are needed to obtain a more accurate answer on the efficacy of treatments for the relief of the signs and symptoms associated with teething.

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