The Role of Sugar-Free Gum in the Management of Orthodontic Pain 24 Hours Following the Application of Orthodontic Force

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Mahmoud Mando

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First reviewer: Prof. Dr. rer. nat. Christoph Bourauel

Second reviewer: PD Dr. Sabine Linsen

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Aus der Poliklinik für Zahnärztliche Prothetik, Propädeutik
und Werkstoffwissenschaften der Universität Bonn
Direktor: Prof. Dr. med. dent. Helmut Stark
- Stiftungsprofessur für Oralmedizinische Technologie -
Prof. Dr. rer. nat. Christoph Bourauel

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List of abbreviations

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICOS	Population, Intervention, Comparison and Outcomes
EBSCO	Elton B. Stephens Company
VAS	Visual Analog Scale
RoB	Risk of Bias
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
RCTs	Randomized Controlled Trials

1. English Summary

1.1 Introduction

Orthodontic treatment is a lengthy, expensive and painful procedure. However, the most frequent side effect of orthodontic therapy as reported by 90 % of orthodontic patients is being painful experiences (Otasevic et al., 2006). One third of patients receiving orthodontic treatment considered ending their treatment prematurely (Otasevic et al., 2006). Therefore, pain is considered a concerning factor during orthodontic treatment, which negatively affects the patients' level of compliance and alters their attitude towards completing treatment (Jones, 1984; Oliver and Knapman, 1985). Various orthodontic procedures are frequently accompanied by pain. These include placement of separators (Jones, 1992), fixed appliance therapy (Needelman et al., 2000) as well as removable appliance therapy (Bondemark and Fredriksson, 2004).

The overall perception of pain among patients who received fixed appliance therapy was 91 % (Scheurer et al., 1996), and more than one third of patients reported pain at specific stages of treatment (Lew, 1993). As compared to removable appliance therapy, fixed appliance therapy generated more pain during the first four days following initial archwire activation (Wiedel and Bondemark, 2016). Usually, the pain intensity reaches its peak one day after the insertion of separators or archwires and starts to decline gradually over a period of 7 days (Wilson et al., 1989). On the contrary to this, in some studies, it was shown that nearly 50 % of patients continued to perceive pain even 7 days following the placement of an archwire (Bergius et al., 2002).

In several studies it was shown that the resulting pain during orthodontic therapy has a negative influence on daily life (Bergius et al., 2002; Scheurer et al., 1996). This negative influence is mainly manifested as psychological irritation (Bergius et al., 2002). Moreover, jaw function, swallowing and speech may be altered during treatment (Fledmann et al., 2012; Stewart et al., 1997). In addition, reduced masticatory function is reported by patients one day following the insertion of archwires and lasts 4 to 6 weeks (Fledmann et al., 2012; Trein et al., 2013). The application of orthodontic forces induces a series of inflammatory events. During these events, inflammatory mediators such as prostaglandin, serotonin, bradykinin, and substance P are released to initiate orthodontic tooth movement. These inflammatory mediators are responsible

for the induction of pain (Arias et al. 2006; Krischnan and Davidovitch, 2006). To reduce pain and discomfort brought on by orthodontic treatment, orthodontists prescribe several analgesics such as paracetamol, ibuprofen and acetylsalicylic acid (Bradley et al., 2007; Karthi et al., 2012). However, these analgesics have contraindications and side effects (Jones, 1984). Additionally, they might negatively influence the orthodontic tooth movement by interfering with the inflammatory process responsible for initiating it (McAlinden et al., 2005).

Proffit argued that the action of repetitive chewing associated with chewing sugar-free gum can reduce ischemia by generating compression and decompression-cycles of the periodontal ligaments, thus reducing orthodontic pain (Proffit et al., 2007). Therefore, chewing gum might be an effective non-pharmacological intervention to reduce pain during orthodontic treatment. In addition, sugar-free gum has been utilized in dentistry for a variety of therapeutic applications. It can be used to increase salivary flow in patients with dry mouth (Kaae et al., 2020), helps in lowering bleeding score, gingivitis and plaque buildup (Aheer et al., 2019), as well as it can be used to assess masticatory function and improve oral function in older adults (Arakawa et al., 2020; Kugimiya et al., 2021). Furthermore, several papers emphasized that surgical recovery after ileus surgical interventions can be enhanced through chewing gum (Nelson et al., 2019; Wallstrom and Frisman, 2014).

It has not been well investigated how chewing gum can help with the pain related with orthodontic therapy. Therefore, by combining data from the available literature, the aim of this study was to evaluate the efficacy of chewing gum in alleviating orthodontic pain during fixed appliance therapy, draw a better conclusion about the connection between orthodontic pain and chewing gum and direct future research to develop a better understanding of the link between the two.

1.2 Materials and Methods

1.2.1 PICOS Model

To define the necessary information needed to formulate a clinical question as suggested by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) system, a PICOS (Population, Intervention, Comparison, Outcomes and Study design) model was implemented with the following parameters:

Population: patients aged 12 years old and above undergoing fixed orthodontic therapy;

Intervention: sugar-free gum to control orthodontic pain;

Comparison: patients with the same age group as the population, but receive different intervention to control pain during fixed orthodontic therapy;

Outcome: the reported pain intensity 24 hours following the application of orthodontic force;

Study design: only randomized controlled trials (RCTs) were considered.

1.2.2 Protocol and Registration

To avoid duplication of studies and ensure the novelty of this systematic review, the online database of the International Prospective Register of Systematic Reviews (PROSPERO) was checked thoroughly for similar topics, then this review was registered in the PROSPERO and was assigned the following reference number CRD42019141501. This study was reported in compliance with the PRISMA guidelines for systematic reviews and meta-analysis.

1.2.3 Information Sources and Search Strategy

A broad search approach was implemented to extract relevant studies, since chewing gum has been recently introduced in orthodontic treatment as a suggested method to alleviate orthodontic pain. This search approach included a combination of systematic electronic search and manual hand search of specific pioneer journals. The electronic search of databases was conducted in Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ScienceDirect and EBSCO (Elton B. Stephens Company) up to September 2022 using the following keywords: “non-pharmacological interventions" AND “orthodontic pain”; “non-pharmacological interventions” AND “orthodontic pain” OR “pain reduction” OR “pain control” OR “Pain management”; “chewing gum” OR “sugar-free gum” AND “orthodontic pain”. The manual hand search was carried out using hard copies of the following journals in orthodontics: Angle Orthodontist; Journal of Orofacial Orthopedics / Fortschritte der Kieferorthopädie; European

Journal of Orthodontics; American Journal of Orthodontic and Dentofacial Orthopedics. Hard copies of studies published in these journals between 2010 and 2022 were carefully inspected for possible inclusion. The manual hand search aimed at inspecting high-impact journals to identify articles which might be unindexed or inaccurately indexed, thus reducing the possibility to eliminate these studies by chance.

1.2.4 Eligibility Criteria

The inclusion and exclusion criteria as seen were carefully inspected. Only RCTs that fulfilled the inclusion and exclusion criteria were considered for further analysis. These RCTs compared patients who received fixed orthodontic therapy to correct malocclusion; aged 12 years old and more; not consuming analgesics or antibiotics; have no contraindications to taking analgesics or chewing sugar-free gum during treatment and receive sugar-free gum to manage the resulting pain during treatment to those in the same age group who receive different intervention or no intervention at all. To determine the eligibility of potential articles, two authors evaluated them independently and in duplicate. Titles, abstracts, full texts as well as references of these studies were thoroughly inspected to evaluate their potential to meet the inclusion criteria.

1.2.5 Primary Outcome Assessment

The peak pain intensity recorded by participants using a visual analogue scale (VAS) 24 hours following the insertion of archwires was considered the primary outcome. The peak pain intensity was reported by the participants using a 10 cm or 100 mm VAS or 10 points rating scale. To create a standardized assessment tool, the 100 mm VAS was converted to a 10 cm scale and the 10-point rating scale was considered similar to the 10 cm VAS. The same approach to combine these assessment tools into a single numerical scale was implemented in a recent study (Mbizvo et al., 2015). When needed, a single measurement of pain intensity at 24 hours was created by combining VAS scores reported at different functions including fitting back teeth or front teeth together, chewing or when jaws are at rest as recommended by the Cochrane handbook for systematic reviews of interventions (Higgins and Green, 2011).

1.2.6 Data Extraction and Meta-Analysis

Items were collected by two authors independently, then the extracted items were entered into Microsoft Excel 2016. The following items were extracted from each RCT: authors, year of publication, participants' gender, age and dropout, intervention, instructions, method of pain assessment, author's conclusion. Disagreement was resolved through detailed discussion between the authors. An effort was made to contact the authors of the included studies in case there were any missing data or unanswered questions regarding these studies.

To run the statistical analysis, a Cochrane collaboration tool represented by Review-Manager (Revman 5.4.1) software was used to run the meta-analysis (The Cochrane Collaboration, 2020). The following data were pooled from each study and entered into this software. These data include the sample size, the means of perceived VAS scores reported by the participants 24 hours following the insertion of archwires, and their corresponding standard deviations. The standardized mean difference (SMD) was inspected, and the corresponding 95 % confidence interval was estimated for the effect size. To test for the heterogeneity in this meta-analysis, a Q statistic was conducted, and to test for the across-studies heterogeneity, I-square statistic was implemented (Deeks et al., 2020).

1.2.7 Risk of Bias in Individual Trials

The Cochrane RoB (Risk of Bias) tool was implemented by two authors independently to assess the degree of bias in each included RCT in this review (Higgins et al., 2011). Again, any disagreement was resolved through discussion. The level of certainty of evidence and the overall risk of bias was evaluated for each individual meta-analysis using the Grade (Grading of Recommendations, Assessment, Development and Evaluation) approach tool (Balshem et al., 2011).

1.3 Results

1.3.1 Study Selection and Characteristics

The number of articles which were included or excluded at different stages of this review was reported in Figure 1 of the publication. A total of 419 studies were identified including 413 studies via databases und 6 studies via other methods, these include 4 from manual hand search and 2 by checking references of the included studies. After duplicates were removed, 29 studies were evaluated for inclusion in this review. After careful inspection of the titles, abstracts as well as full texts of these papers, 13 studies were not considered for further inclusion in this review. These excluded studies consisted of 12 reviews and 1 case control study. Finally, 16 RCTs were included in this review for final analysis. Table 1 of the publication summarizes the main characteristics of these studies.

1.3.2 Risk of Bias within Studies

Using the Cochrane RoB tool as depicted in figure 2 and figure 3 of the publication, the quality of evidence of Alqareer 2019 study was assessed at high risk of bias. This was due to the lack of blinding of study's participants and high withdrawal rate which resulted in incomplete data, in addition to improper gender distribution between groups (Alqareer et al., 2019). Similarly, the Farzanegan 2012 study was assessed at high risk of bias since allocation concealment was unclear, blinding the outcome assessors as well as blinding the participants and personals were not possible, in addition to the high risk of bias of other biases including the recruitment of female participants only (Farzanegan et al., 2012).

Furthermore, the Waheed-Ul-Hamid 2016 and the Azeem 2018 studies were assessed at unclear risk of bias since allocation concealment, blinding the participants and personnel and blinding the outcome assessors were unclear (Azeem et al., 2018; Waheed-Ul-Hamid et al., 2016). Similarly, the Celebi 2021 study was assessed at unclear risk of bias due to unclear sequence of randomization, allocation concealment, blinding the participants and personnel and blinding the outcome assessors (Celebi et al., 2021). Both the Nadeem 2016 study and the Celebi 2022 study were assessed at unclear risk of bias due to unclear allocation concealment and unclear blinding of the participants and personnel and blinding the outcome assessors (Celebi, 2022;

Nadeem et al. 2016). The Al-Shayea 2020 study was assessed at high risk of bias due to unclear allocation concealment, blinding the participants and personnel and blinding the outcome assessors. In addition, there was a high risk of other biases due to including female participants only (Al-Shayea, 2020). Similarly, the Basam 2022 study has also included female participants only with a lack of blinding the participants and personnel as well as blinding the outcome assessors. Therefore, it was assessed at high risk of bias (Basam et al., 2022). On the other hand, the Dalavarian and Iman 2020 study was assessed at moderate risk of bias due to unclear allocation concealment and absence of blinding of participants (Delavarian and Iman, 2020). The Rossi study 2022 was assessed at moderate risk of bias due to unequal gender distribution and unclear blinding of both the participants and personnel as well as the outcome assessors (Rossi et al., 2022). The Abdul-Aziz study 2022 was assessed at moderate risk of bias due to lack of blinding the participants and personnel and blinding the outcome assessors (Abdul-Aziz, 2021).

The Benson 2012 study was assessed at high risk of bias due to the absence of blinding the outcome assessors as well as blinding the participants and personals were not possible. In addition, there was a high risk of bias of other biases including unequal distribution between groups (Benson et al., 2012), even though the randomization used in this study should have eliminated this type of bias. The remaining studies were also assessed as high risk of bias (Al-Shammari and Huggare, 2019; Da Silva Santos and Capelli, 2021; Ireland et al., 2016).

According to the GRADE tool, the quality of evidence across studies was very low (Table 2. of the publication).

1.3.3 Results of Individual Studies

1.3.3.1 Chewing Gum vs. Pharmacological Agents

As shown in Figure 4 of the publication, seven RCTs (Alshammari and Huggare, 2019; Al Shayea, 2020; Azeem et al., 2018; Delavarian and Iman, 2020; Franzanegan et al., 2012; Ireland et al., 2016; Waheed-Ul-Hamid et al., 2016) investigated the impact of chewing sugar-free gum and pharmacological agents (Ibuprofen and Paracetamol) on pain relief one day following the placement of an initial archwire. A statistically significant study heterogeneity was detected [$x^2 = 49.19$, $I^2 = 88\ \%$ ($P < 0.00001$)]. Therefore,

a random effect model was used to conduct the analysis. A statistically significant difference in the relief of pain was found between the chewing gum and the pharmacological agents including Ibuprofen and Paracetamol with a standardized mean difference (SMD) of -0.50 [(-0.90, -0.10), P= 0.01].

1.3.3.2 Chewing Gum vs. Placebo

As shown in Figure 5 of the publication, four RCTs (Alqareer et al., 2019; Celebi et al., 2021; Delavarian and Iman, 2020; Franzanegan et al., 2012) investigated the impact of chewing sugar-free gum and a placebo on pain relief one day following the placement of an initial archwire. No statistically significant study heterogeneity was detected [$x^2 = 5.34$, $I^2 = 44\%$ ($P = 0.15$)]. Therefore, a fixed effect model was used to conduct the analysis. A statistically significant difference in the relief of pain was found between the chewing gum and the placebo with a standardized mean difference (SMD) of -0.58 [(-0.92, -0.23), P=0.01].

1.3.3.3 Chewing Gum vs. Hard Viscoelastic Bite Wafer

As shown in Figure 6 of the publication, two RCTs (Al Shayea, 2020; Franzanegan et al., 2012) investigated the impact of chewing sugar-free gum and a hard viscoelastic bite wafer on pain relief one day following the placement of an initial archwire. No statistically significant study heterogeneity was detected [$x^2 = 0.05$, $I^2 = 0\%$ ($P = 0.82$)]. Therefore, a fixed effect model was used to conduct the analysis. No statistically significant difference in the relief of pain was found between the chewing gum and the hard viscoelastic bite wafer with a standardized mean difference (SMD) of -0.15 [(-0.56, -0.26), P=0.48].

1.4 Discussion

Four RCTs were considered in the qualitative analysis due to reporting median VAS scores of pain and not the means. According to Benson et al., no statistically significant difference in the median VAS was found between non-intervention group and those who received chewing gum (Benson et al., 2012). However, with more female

patients in the group that did not chew gum and more male patients in the group did, the gender distribution in this study was unequal between the two groups. Additionally, participants were told to use painkillers if necessary in all groups, while those in the chewing gum group were instructed to consume sugar-free gum in the event of pain. According to Da Silva Santos and Capelli, patients who were assigned to chewing gum group and those who were assigned to pharmaceutical drugs group experienced different levels of pain throughout various functions. The patients in the Ibuprofen group reported more pain while jaw at rest and during biting as compared to the patients in the chewing gum group and the patients in the Paracetamol and control groups reported more pain during biting as compared to those in the chewing gum group (Da Silva Santos and Capelli, 2021). Basam et al. compared the pain levels experienced by patients who were assigned to chew sugar-free gum and those who were instructed to take 20 mg of Tenoxicam during various functions 24 hours following the insertion of initial wires, patients in the Tenoxicam group reported more pain when chewing, and those in the chewing gum group reported more discomfort when biting and fitting their back teeth together. This difference in pain intensity between the two groups was not statistically significant (Basam et al., 2022).

According to Celebi, there was no statistically significant difference between chewing gum, mechanical vibration, and control group at any point throughout the treatment (Celebi, 2022). However, it can be argued that compared with other RCTs in this review, the participants in that study had less exposure to the intervention during treatment, as they were only asked to chew sugar-free at three time points during the entire treatment. Furthermore, Rossi et al. found that there was no statistically significant difference between placebo, chewing gum, or Ibuprofen in terms of reducing the severity of pain experienced during initial orthodontic treatment (Rossi et al., 2022).

Abdul-Aziz compared the reduction in pain intensity between patients who were instructed to chew sugar-free gum for 1 week to those who did not receive any intervention. The results of this study revealed that chewing sugar-free gum three times a day was an effective intervention in the reduction of pain over a period of one week when compared to no intervention (Abdul-Aziz, 2021). Similarly, chewing gum was able to reduce the intensity of pain 24 hours following the insertion of archwires and this effect was seen over a period of one week (Nadeem et al., 2016).

The findings of the current meta-analysis revealed a statistically significant reduction in the intensity of pain 24 hours following the insertion of archwires between the chewing gum and the pharmaceutical agents as well as between the chewing gum and the placebo.

Wiedel and Bondemark conducted a RCT to compare the difference in the perceived pain by patients undergoing different treatment modalities in orthodontics. Wiedel and Bondemark revealed that patients who received fixed orthodontic treatment reported more pain intensity during the first few days following the application of archwire as compared to patients who received removable orthodontic treatment (Wiedel and Bondemark, 2016). Therefore, chewing gum alone or in conjunction with analgesics can help patients undergoing fixed orthodontic treatment by reducing pain, enhancing quality of life, and consuming less analgesics.

The perceived pain during different jaw functions has only been reported in a few studies (Alshammari and Huggare, 2019; Franzanegan et al., 2012; Rossi et al., 2022). However, the intensity of reported pain during orthodontic treatment varies from function to function and when the jaws are not active (Alshammari and Huggare, 2019). Therefore, to obtain a better understanding of the specific role of chewing gum in the reduction of orthodontic pain, we recommend future studies to evaluate its role during different jaw functions.

1.4.1 Limitations

The results of the current meta-analysis were synthesized 24 hours following the insertion of an archwire since the pain intensity reaches its peak one day after the insertion of separators or archwires and starts to decline gradually over a period of 7 days (Wilson et al., 1989). However, some studies reported that nearly 50 % of patients continued to perceive pain even 7 days after the insertion of an archwire (Bergius et al., 2002). We attempted to investigate the difference in pain intensity at multiple points during the treatment, but this was impossible since majority of the included studies reported the mean VAS of pain at different time points. Therefore, we recommend future studies to investigate the role of chewing sugar-free gum in the reduction of orthodontic pain at multiple and similar time points.

Furthermore, the high risk of bias among the included studies as revealed by the Cochrane RoB tool and the very low quality of evidence according to the GRADE approach suggest the need for high quality and well-designed RCTs.

1.5 Abstract

The aim of this study was to investigate the role of chewing gum in alleviating orthodontic pain during fixed appliance therapy. A broad search approach was implemented which included a combination of systematic electronic search and manual hand search of specific pioneer journals. The electronic search of databases was conducted in Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ScienceDirect and EBSCO up to September 2022. The degree of bias in each included randomized controlled trial in this review was assessed using the Cochrane risk of bias tool and the level of certainty of evidence and the overall risk of bias was evaluated for each individual meta-analysis using the Grade approach tool. After duplicates were removed, 29 studies were evaluated for inclusion in this review. Of these studies, only 16 randomized controlled trials were included in this review for final analysis. The results of this analysis showed a statistically significant reduction in pain intensity between chewing gum and pharmacological interventions (SMD) of -0.50 [(-0.90, -0.10), P= 0.01], a statistically significant reduction in pain intensity between chewing gum and placebo (SMD) of -0.60 [(-1.06, -0.13), P=0.01] and no statistically significant difference between chewing gum and bitewafer (SMD) of -0.15 [(-0.56, 0.26), P=0.48]. Therefore, to reduce orthodontic pain elicited 24 h after archwire activation, pharmacological agents such as Ibuprofen and Paracetamol can be substituted with chewing gum.

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2. Publication in The Angle Orthodontist

The Efficacy of Chewing Gum in the Reduction of Orthodontic Pain at its Peak Intensity: A Systematic Review and Meta-Analysis

Mahmoud Mando, Sameh Talaat, Christoph Bourauel

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Systematic Review Article

The efficacy of chewing gum in the reduction of orthodontic pain at its peak intensity: a systematic review and meta-analysis

Mahmoud Mando[a]; Sameh Talaat[b]; Christoph Bourauel[c]

ABSTRACT

Objectives: To evaluate the efficacy of chewing gum on the intensity of pain in patients undergoing orthodontic treatment.

Materials and Methods: A search strategy that included both a manual search and a search of electronic databases was implemented; the electronic databases included PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, Scopus, and EBSCO. Only randomized controlled trials were included in this study. All of the studies were assessed independently and in duplicate in accordance with the exclusion and inclusion criteria. The Cochrane risk of bias tool was used to evaluate the risk of bias within the included studies, and the GRADE approach was used to evaluate the certainty of evidence.

Results: Sixteen RCTs were included in the final analysis. The meta-analysis revealed that chewing gum significantly reduced pain intensity in comparison to pharmacologic agents (mean difference [MD] −0.50 [95% confidence interval {CI} −0.90 to −0.10], $P = .01$). When compared with a placebo, chewing gum significantly reduced pain intensity (MD −0.60 [95% CI −1.06 to −0.13], $P = .01$), while bite wafer and chewing gum groups had the same levels of reduction in pain intensity (MD −0.15 [95% CI −0.56 to 0.26], $P = .48$).

Conclusions: In patients undergoing fixed orthodontic treatment, chewing gum was significantly more effective than both pharmacologic agents and placebo in reducing orthodontic pain 24 hours after the initial placement of the archwire. (*Angle Orthod.* 2023;93:580–590.)

KEY WORDS: Orthodontics; Orthodontic pain; Chewing gum; Pharmacologic interventions

INTRODUCTION

Orthodontic treatment often comprises long-lasting, painful, and expensive procedures. Pain is considered the main reason why patients interrupt their treatment, and it negatively influences their level of compliance.[1,2] Different types of orthodontic procedures usually cause pain. These procedures include archwire activation,[3] orthopedic appliances,[4] and the placement of separators.[5] Among patients undergoing fixed orthodontic treatment, 91% complained of pain at some stage of the treatment,[6] and more than 30% of patients reported pain at each stage during the course of treatment.[7] Pain was reported to be the main discouraging reason to discontinue treatment.[2] Therefore, orthodontic pain is a major concern for both orthodontists and patients. It was shown that, in most patients, the peak intensity of pain occurred 1 day following the insertion of an archwire or separators and decreased gradually over the next 7 days.[8] On the other hand, in some studies, it was reported that almost half of patients experienced orthodontic pain even 1 week after the insertion of an archwire.[9]

Orthodontic tooth movement is an inflammatory process that occurs following the application of orthodontic force. During this inflammatory process, several inflammatory mediators, including substance P, prostaglandin, bradykinin, serotonin, and histamine, are released after a series of biological events. In turn, these mediators induce pain by stimulating nerve endings.[10,11] Ibuprofen, acetylsalicylic acid, and para-

[a] Doctoral Degree Student, Department of Oral Technology, University of Bonn, Bonn, Germany; Researcher, Health Research Institute, Faculty of Public Health, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

[b] Lecturer, College of Dentistry, Future University in Egypt, New Cairo, Egypt; and Associate Research Scientist, Department of Oral Technology, University of Bonn, Bonn, Germany.

[c] Professor, University Hospital Bonn and Oral Technology, University of Bonn, Bonn, Germany.

Corresponding author: Dr Mahmoud Mando, Department of Oral Technology, University of Bonn, Bonn 53127, Germany (e-mail: m_mando1995@outlook.com)

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cetamol are the analgesics most commonly prescribed by orthodontists to alleviate pain and discomfort caused by orthodontic treatment.[12–14] On the other hand, these pain relievers may interfere with the inflammatory process responsible for inducing orthodontic tooth movement.[15] In addition, these analgesics have negative side effects and contraindications.[14,15]

The repetitive chewing action performed while chewing gum can reduce orthodontic pain by reducing ischemia through the compression and decompression of the PDL.[16] Thus, chewing sugar-free gum may be a promising nonpharmacologic intervention that reduces orthodontic pain. In addition, sugar-free gum has different uses in dentistry. It can be used as a salivary substitute to improve salivary flow and relieve the symptoms of dry mouth[17]; reduce plaque accumulation, gingivitis, and bleeding score[18]; and it can be used to evaluate chewing function in adults and the elderly.[19,20] Also, several articles emphasized that chewing gum may enhance surgical recovery following postoperative ileus surgical interventions.[21–23]

The aim of this study was to synthesize evidence from the existing literature to explore fully the efficacy of chewing gum in reducing pain intensity in patients undergoing fixed orthodontic treatment, evaluate the quality of evidence of the existing literature and direct future research to develop an improved conclusion regarding the relationship between chewing gum and orthodontic pain.

MATERIALS AND METHODS

A well-structured design was implemented using the PICOS methodology:

- Population: patients aged 12 years or older who were receiving fixed orthodontic treatment
- Intervention: chewing gum
- Comparison: patients receiving different intervention or no treatment
- Outcome: reduction in reported pain intensity 24 hours after the activation of orthodontic force
- Design: randomized clinical trials (RCTs)

Protocol and Registration

The systematic review was registered in Prospero (International Prospective Register of Systematic Reviews) with reference number CRD42019141501 and was reported in adherence to the Prisma checklist guidelines.

Information Sources and Search Strategy

In this systematic review, a comprehensive search strategy was used, which started in September 2021 and ended in September 2022 and incorporated both electronic and manual search methods. The electronic database search included PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, EBSCO, and ScienceDirect. In addition, a thorough manual search was performed to identify articles that were not indexed in databases and to eliminate any chance of excluding related articles.

Journals Manually Searched

The following journals were included in the manual search:

- *European Journal of Orthodontics* (2010–2022)
- *Angle Orthodontist* (2010–2022)
- *American Journal of Orthodontic and Dentofacial Orthopedics* (2010–2022)
- *Journal of Orofacial Orthopedics/Fortschritte der Kieferorthopädie* (2010–2022)

Eligibility Criteria

After the careful inspection of articles in accordance with the exclusion and inclusion criteria, only randomized controlled articles that involved patients who were (1) a minimum age of 12 years old, (2) receiving chewing gum as an intervention to control orthodontic pain, (3) undergoing fixed orthodontic treatment, (4) reporting pain 24 hours following the application of orthodontic force, (5) medically fit, (6) with no contraindication to use chewing gum or analgesics, and (7) currently not consuming analgesics or antibiotics, were considered in this study. Potential articles were assessed independently and in duplicate by two authors to determine their eligibility to meet the inclusion criteria; the titles, abstracts, and full texts of these articles were carefully assessed. In addition, the references of these articles were reviewed thoroughly to assess their eligibility to meet the inclusion criteria.

Primary Outcome Assessment

The intensity of orthodontic pain reported by patients 1 day after the insertion of an initial archwire was the primary outcome. A visual analog scale (VAS) reported on a 100-mm or a 10-cm scale and a numeric rating scale out of 10 points were used as the outcome assessment tool. In a recent article, the same method of combining these 10-point numerical scales into a single scale was used.[24] VAS values reported from multiple functions (while fitting front teeth or back teeth together, while chewing, or when jaws were at rest) were combined into a single estimate using a formula to combine groups, as suggested in the Cochrane handbook of systematic reviews of interventions.[25]

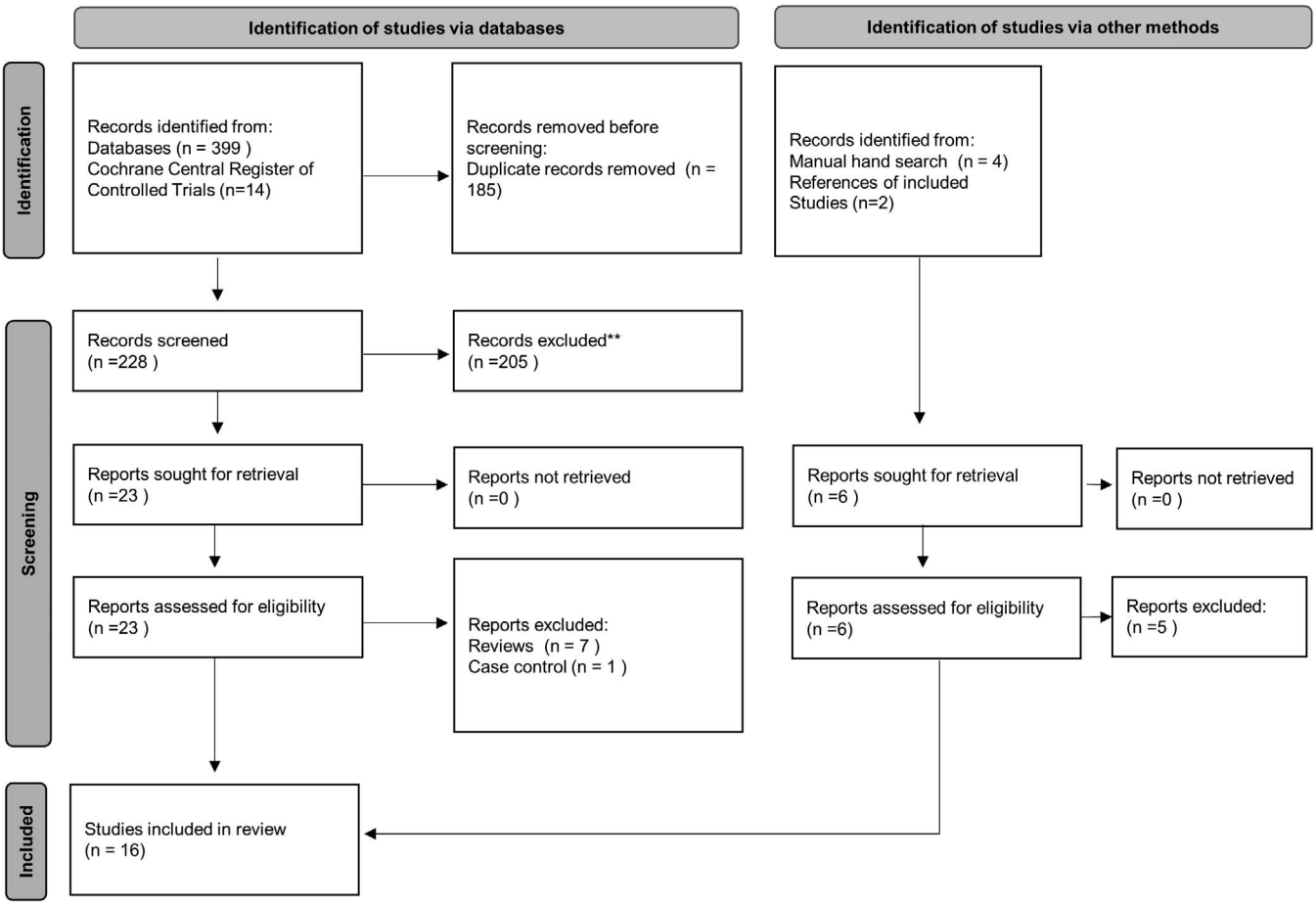

Figure 1. Flowchart showing the process of including and excluding studies at different phases.

Data Extraction and Meta-analysis

For the purpose of statistical analysis, two authors performed data extraction from each included study. The extracted data were later entered into Microsoft Excel 2016. The mean VAS reported by patients in each group 1 day after the insertion of the initial archwire, the sample size, and the standard deviation of the mean VAS represented the extracted data. The extracted data were entered into ReviewManager (Revman 5.4.1) software, which is a Cochrane collaboration software designed to run meta-analyses. The standardized mean difference (SMD), also known as effect size or Cohen's *d*, was inspected, and the corresponding 95% confidence intervals were estimated for the effect sizes. The Q statistic was conducted to test for heterogeneity in this meta-analysis, and the between-study heterogeneity was assessed using the I^2 statistic.

Risk of Bias in Individual Trials

To assess the level of bias among the studies included, two authors evaluated them thoroughly and independently using the Cochrane risk of bias tool.[26] The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[27]

RESULTS

Study Selection and Characteristics

The flowchart in Figure 1 illustrates how many articles were excluded and included at different phases. The total number of studies assessed was 419, and of these, 413 studies were obtained from the electronic search, 4 from the manual search, and 2 by checking the reference lists of the studies included. Following the elimination of duplicates, 29 studies were assessed for possible inclusion in this review. A thorough review of the full texts of these articles led to the exclusion of 13 studies, including 1 case control and 12 reviews. As a result, 16 RCTs were considered in this review. The main characteristics of the studies are shown in Table 1.

Table 1. Summarized Published Data of the Studies Included in the Systematic Review

Study ID	Participants' Size, Gender, Age (y), Dropout	Interventions	Instructions	Method of Pain Assessment	Author Conclusion
Basam et al. 2022[31]	N = 42 (only females); 2 dropouts	Group 1 Chewing gum Mean age = 19.6 y Group 2 Tenoxicam Mean age = 20 y	Group 1 Chew sugar-free gum 10 to 12 min whenever you experience pain Group 2 20 mg tenoxicam 1 h before archwire placement	VAS	There was no statistically significant difference between the two groups. Chewing gum was not inferior to tenoxicam.
Celebi 2022[41]	N = 57 (27 males, 30 females); no dropouts	Group 1 Mechanical vibration Mean age = 14.1 y Group 2 Chewing gum Mean age = 15.1 y Group 3 Control group Mean age=15.2	Group 1 N/A Group 2 Chew sugar-free gum for 20 min After initial wire placement, after 24 h and after 48 h Group 3 No intervention	VAS	As compared with the chewing gum, the mechanical vibration has no clinically significant pain relief effect during orthodontic treatment.
Rossi et al. 2022[36]	N = 102 (59 females, 30 male); 13 dropouts	Group 1 Placebo Group 2 Chewing gum Group 3 Ibuprofen	Group 1 Capsules containing harmless material 1 h after initial wire placement and every 8 h Group 2 Chew sugar-free gum for 10 min every 4 h Group 3 400 mg of ibuprofen 1 h after initial wire placement and every 8 h	VAS	No difference between the three methods was observed. Chewing gum may be used adequately for orthodontic pain.
Abdul-Aziz 2021[37]	N = 60 (24 males, 29 females); 7 dropouts	Group 1 Chewing gum Mean age = 21.8 y Group 2 No intervention Mean age = 22.3 y	Group 1 Chew sugar-free gum 10 min every 8 hours and immediately after separator placement. Group 2 No intervention	VAS	Compared with the non–chewing gum group, chewing gum reduced pain significantly.
Celebi et al. 2021[40]	N = 63 (30 males, 33 females); no dropouts	Groups 1 Laser Mean age = 15.4 y Group 2 Chewing gum Mean age = 15.8 y Control group 3 No intervention Mean age = 15.3 y	Group 1 N/A Group 2 Chew sugar-free gum 20 min three times per day. Group 3 Control group with no intervention	VAS	There was no statistically significant difference between the three groups at any time of treatment.
da Silva Santos and Capelli 2021[35]	N = 106 (52 males, 54 females); 25 dropouts	Group 1 Chewing gum Mean age = 16.6 y Group 2 Ibuprofen Mean age = 19.2 y Group 3 Acetaminophen Mean age = 19.5 y Group 4 Control Mean age 18.5	Group 1 Chew sugar-free gum 5 min every 6 h and immediately after archwire placement Group 2 Ibuprofen 400 mg every 6 h and immediately after archwire placement Group 3 Acetaminophen 500 mg every 6 h and immediately after archwire placement Group 4 Control group with no intervention	VAS	Patients in the chewing gum group experienced less pain during biting and at rest compared with the ibuprofen group and less pain at biting when compared with control and acetaminophen groups.

Table 1. Continued

Study ID	Participants' Size, Gender, Age (y), Dropout	Interventions	Instructions	Method of Pain Assessment	Author Conclusion
Al Shayea et al. 2020[30]	N = 105 (90 females); 15 dropouts	Group 1 Ibuprofen Mean age = 24.7 y	Group 1 Ibuprofen 400 mg three times per day and immediately after archwire placement	VAS	The experience of pain between all groups was similar. Thus, chewing gum can be used to replace ibuprofen.
		Group 2 Viscoelastic Bite wafer Mean age = 21.8 y	Group 2 Chew on viscoelastic bite wafer three times per day for 5 min Bite wafer		
		Group 3 Chewing gum Mean age = 25.9 y	Group 3 Chew sugar-free gum for 5 min three times per day		
Delavarian and Imani 2020[38]	N = 66 (15 males, 35 females); 6 dropouts	Group 1 Placebo Mean age = 18.9 y	Group 1 Placebo 40 mg of vitamin B_{12} three times per day and immediately after archwire placement	NRS	Patients in the placebo group reported higher pain than those in the chewing gum or the ibuprofen groups. Chewing gum can be used as an alternative to ibuprofen.
		Group 2 Ibuprofen Mean age = 20.25 y	Group 2 Ibuprofen 400 mg three times per day and immediately after archwire placement		
		Group 3 Chewing gum Mean age = 19.8 y	Group 3 Chewing gum Chew sugar-free gum for 10 min three times per day		
Alqareer et al., 2019[29]	N = 75 patients (10 males, 25 females); 40 dropouts	Group 1 Chewing gum Mean age = 16.9 y	Group 1 Chew sugar-free chewing gum 5–10 min three times per day	VAS	Chewing gum does not significantly reduce orthodontic pain compared with placebo.
		Group 2 Placebo Mean age = 16.1 y	Group 2 Rinse for 30 s with a fluoridated, alcohol-free mouth wash (Plax sensitive) three times per day		
Alshammari and Huggare 2019[33]	N = 60 patients (28 males, 32 females); 15 dropouts	Group 1 Chewing gum Mean age = 14.2 y	Group 1 Chew gum 10 minutes 3 times per day.	VAS	Chewing gum and paracetamol are equivalent in the reduction of orthodontic pain without having any negative effect on bracket loss.
		Group 2 Paracetamol Mean age = 14.3 y	Group 2 Paracetamol 1000 mg or 500 mg three times per day if patient weighs less than 40 kg		
Azeem et al., 2018[39]	N = 120 (54 males, 66 females); no dropouts	Group 1 Chewing gum Mean age = 15.6 y	Group 1 Chew sugar-free gum 5 minutes three times per day and immediately after separator placement	VAS	Chewing gum can be recommended as a nonpharmacologic option instead of ibuprofen for orthodontic pain control associated with separator placement.
		Group 2 Ibuprofen Mean age = 15.5 y	Group 2 Ibuprofen 400 mg four times per day and 1 h before separator placement		
Ireland et al., 2016[34]	N = 1000 (370 males, 630 females); 164 dropouts	Group 1 Chewing gum Mean age = 13.7 y	Group 1 Chew gum for pain relief if required and ibuprofen 250 mg if chewing gum is not effective	VAS	The use of sugar-free chewing gum after fixed appliance placement reduces the need for ibuprofen without having any significant effect on the bracket.
		Control group 2 Ibuprofen Mean age = 13.6 y	Group 2 Ibuprofen 250 mg when required		

Table 1. Continued

Study ID	Participants' Size, Gender, Age (y), Dropout	Interventions	Instructions	Method of Pain Assessment	Author Conclusion
Ul-Hamid et al., 2016[42]	N = 250 (133 males, 117 females); mean age 14.03 y; no dropouts	Group 1 Chewing gum Group 2 Ibuprofen	Group 1 Chew a sugar-free gum (Orbit; The Wrigley Company) for 5 min immediately after this and repeated three times per day Group 2 400 mg ibuprofen immediately after first visit and repeated three times per day	VAS	Chewing gum was more effective in reducing orthodontic pain when compared with ibuprofen. This difference in the reduction in pain intensity was statistically significant.
Nadeem et al., 2016[43]	N = 60 (29 males, 31 females); no dropouts	Group 1 Chewing gum Group 2 No intervention	Group 1 Chew sugar-free gum twice daily for 10 min and after initial wire placement Group 2 Control group with no intervention	VAS	A statistically significant reduction in orthodontic pain was reported in the chewing gum group.
Farzanegan et al., 2012[28]	N = 50; 50 females; no dropouts	Group 1 Placebo Group 2 Ibuprofen Group 3 Chewing gum Group 4 Hard wafer Group 5 Soft wafer	Group 1 B_6 vitamin after archwire placement and three times per day for 1 wk Group 2 400 mg ibuprofen after archwire placement and three times per day for 1 wk if pain persisted Group 3 Chew a sugar-free gum (orbit) for 5 min after archwire placement and three times per day for 1 wk Group 4 and 5 Bite on wafer for 5 min three times per day	VAS	Both chewing gum and bite wafer can reduce pain intensity in orthodontic patients and can be used as nonpharmacologic substitutes for ibuprofen.
Benson et al., 2012[32]	N = 57 (31 males, 26 females); no dropouts	Group 1 Chewing gum Mean age = 13.8 y Group 2 No chewing gum Mean age = 14.7 y	Group 1 Chew sugar-free gum (Orbit Complete) when required at the bonding/separator appointments Group 2 Non–chewing gum group was specifically asked not to chew gum for the duration of the study	VAS	Chewing gum reduced pain from fixed orthodontic appliances without causing appliance breakage.

Risk of Bias Within Studies

Figures 2 and 3 illustrate the results of the Cochrane risk of bias tool. According to the quality of the evidence, 10 articles were evaluated as having a high risk of bias,[28–37] 1 article was evaluated as having moderate risk of bias,[38] and 5 articles were evaluated as having unclear risk of bias,[39–43] either due to a lack of information regarding random sequence generation, randomization, allocation concealment, or blinding the outcome assessors and blinding the patients.

The quality of the evidence across studies was evaluated according to the GRADE approach, and it was found that there was a very low quality of evidence (Table 2).

Results of Individual Studies

Chewing gum vs pharmacologic agents. Seven randomized controlled trials[28,30,33,34,38,39,42] compared the effect of chewing gum and pharmacologic agents (ibuprofen and paracetamol) on the reduction in pain 1

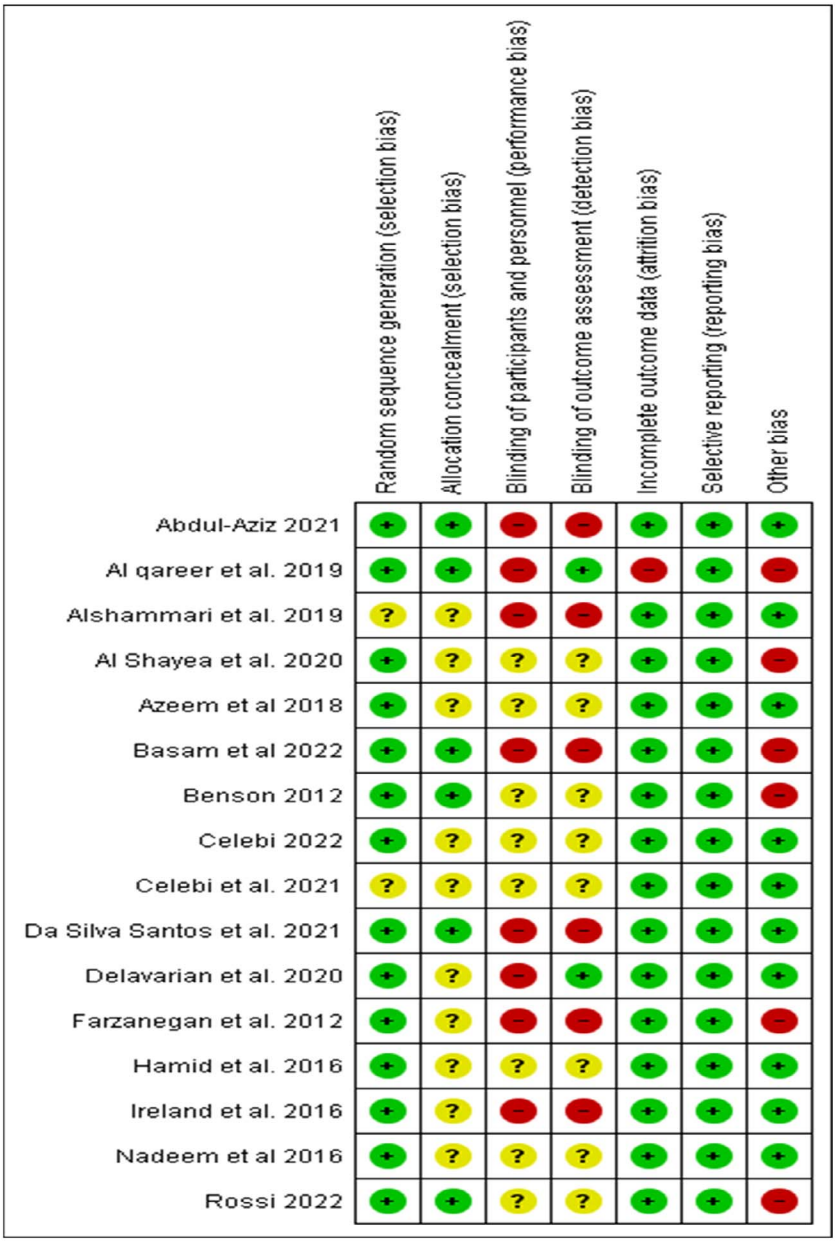

Figure 2. Results of the Cochrane risk of bias tool for quality assessment.

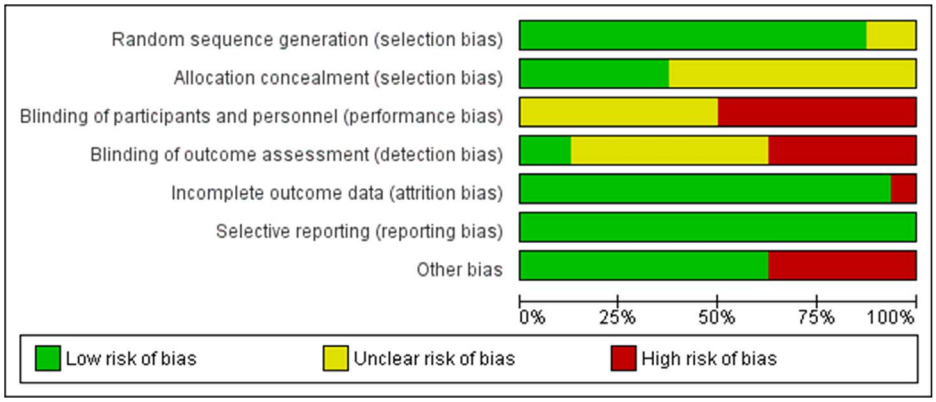

Figure 3. Results of the Cochrane risk of bias tool for quality assessment presented as percentages.

Table 2. Summary of Overall Quality of Evidence of Studies Included in Each Meta-analysis Using GRADE:

	Certainty Assessment							
Outcome	Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Others	Certainty
Chewing gum vs pharmacological agents	7	RCTs	Serious[a]	Serious[b]	Serious[c]	Not serious	Not serious	⊕○○○ Very low
Chewing gum vs placebo	4	RCTs	Serious[a]	Serious[d]	Not serious	Serious[e]	Not serious	⊕○○○ Very low
Chewing gum vs hard bite wafer	2	RCTs	Serious[a]	Serious[f]	Not serious	Serious[e]	Not serious	⊕○○○ Very low

[a] Downgraded due to unclear or absence of blinding of both patients and outcome assessors.
[b] Downgraded due to high heterogeneity ($P < .00001$); $I^2 = 88\%$.
[c] Downgraded due to the inclusion of studies that reported mean pain at 24 h in females only.
[d] Downgraded due to moderate level of heterogeneity; $I^2 = 44\%$.
[e] Downgraded due to small sample size.
[f] Downgraded due to small number of studies and imprecise I^2.

day after the insertion of an initial archwire, as seen in Figure 4. Statistically significant study heterogeneity was found ($\chi^2 = 49.19$, $I^2 = 88\%$; $P < .00001$). Therefore, the analysis was conducted using a random effect model. There was a statistically significant difference in the reduction in pain intensity between the chewing gum and the pharmacologic interventions. The SMD was –0.50 ([–0.90, –0.10], $P = .01$).

Chewing gum vs placebo. Four randomized controlled trials[28,29,38,40] compared the effect of chewing gum and a placebo on the reduction in pain 1 day after the insertion of an initial archwire, as seen in Figure 5. No statistically significant study heterogeneity was found ($\chi^2 = 5.34$, $I^2 = 44\%$; $P = .15$). Therefore, the analysis was conducted using a fixed effect model. There was a statistically significant difference in the reduction in pain intensity between the chewing gum and the placebo. The SMD was –0.60 ([–1.06, –0.13], $P = .01$).

Chewing gum vs hard viscoelastic bite wafer. Only two randomized controlled trials[28,30] compared the effect of chewing gum and a hard viscoelastic bite wafer on the reduction in pain 1 day after the insertion of an initial archwire, as seen in Figure 6. No statistically significant study heterogeneity was found ($\chi^2 = 0.05$, $I^2 = 0\%$; $P = .82$). Therefore, the analysis was conducted using a fixed effect model. No statistically significant difference was found between the hard bite wafer and the chewing gum. The SMD was –0.15 ([–0.56, –0.26], $P = .48$).

DISCUSSION

This was the first meta-analysis to directly investigate the role of chewing gum in the reduction in pain intensity during fixed orthodontic treatment.

Four studies reported median VAS pain scores but not the means. As a result, these studies were excluded from the quantitative analysis. Benson et al.[32] compared patients who received chewing gum to those who did not receive any treatment. There was no statistically significant difference in the median VAS between the two groups.[32] However, this study had an unequal gender distribution between the two groups, with more female participants in the non–chewing gum group and more male participants in the chewing gum group. In addition, the participants in the chewing gum group were instructed to chew only sugar-free gum if needed, and the patients in both groups were instructed to take painkillers if required.

Da Silva Santos and Capelli[35] investigated the difference in pain intensity during different functions between patients who received chewing gum and those who received pharmacologic agents. The patients in the chewing gum group experienced less pain during biting and at rest compared with those who

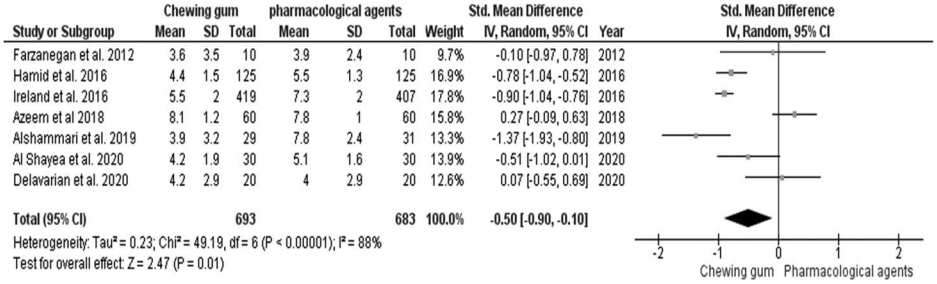

Figure 4. A comparison between chewing gum and pharmacological interventions in decreasing pain intensity.

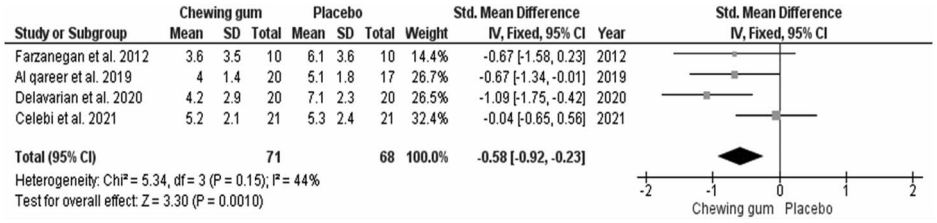

Figure 5. A comparison between chewing gum and placebo in decreasing pain intensity.

received ibuprofen and less pain when biting when compared with the control and acetaminophen groups.[35]

Basam et al.[31] compared the pain intensity between patients who received chewing gum and those who received 20 mg of tenoxicam. Comparing the two groups 1 day after the placement of initial archwires, the patients in the chewing gum group experienced less pain when chewing, and the patients in the tenoxicam group experienced less pain when both biting and fitting their posterior teeth together. However, there was no statistically significant difference between the two groups.[31]

Celebi[41] investigated the difference among mechanical vibration, chewing gum, and control groups. There was no statistically significant difference among the interventions at any time point during the treatment.[41] The results of that study can be questioned due to the participants' minimal exposure to the intervention during treatment as compared with other studies included in this review, as the patients were instructed to chew sugar-free gum for only 20 minutes at three time points.

According to Rossi et al.,[36] the reduction in pain intensity during initial orthodontic treatment caused by ibuprofen, chewing gum, and the placebo was not statistically significant.

Nadeem et al.[43] compared the reported pain intensity between patients in the chewing gum group and those who did not receive any intervention. In the chewing gum group, the median visual analog scale of the reported pain was significantly less after 24 hours and after 1 week of chewing sugar-free gum for 10 minutes twice a day over a period of 1 week.[43] Similarly, patients who received sugar-free gum and were instructed to chew three times a day over a period of 1 week reported a statistically significant decrease in pain intensity compared with patients who received no intervention.[37]

The results of the current meta-analysis revealed a statistically significant reduction in pain intensity after 24 hours of the application of orthodontic force between chewing gum and the placebo as well as chewing gum and pharmacologic agents.

Wiedel et al.[44] investigated the difference in the pain intensity experienced by patients undergoing fixed appliance treatment vs those undergoing removable appliance treatment. The results of that randomized controlled trial revealed that patients undergoing removable appliance therapy experienced less pain intensity in the first few days of treatment compared with those who received fixed appliance therapy.[44] Therefore, patients undergoing fixed orthodontic treatment may benefit from chewing gum alone or in combination with analgesics by alleviating pain, improving quality of life, and reducing analgesic consumption.

In a few studies, the authors reported that pain was experienced by the participants when performing multiple jaws functions,[28,33,36] and it is important to consider that the sensation of pain differs from function to function or when the jaws are at rest.[33] Therefore, future studies should focus more on how chewing gum reduces the pain intensity during different functions in order to gain a better understanding of its role.

In this meta-analysis, the evidence was synthesized 24 hours following the activation of orthodontic force.

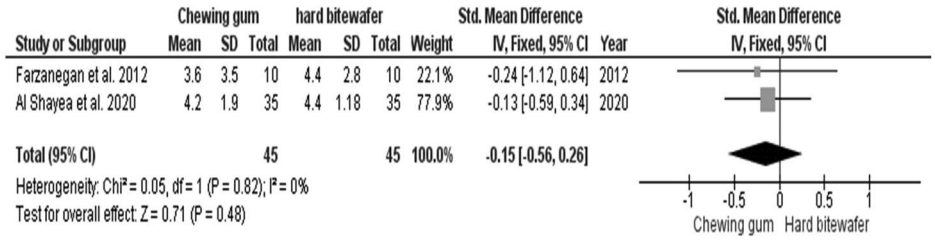

Figure 6. A comparison between chewing gum and viscoelastic bite wafer in decreasing pain intensity.

This limitation can be attributed to differences in reporting the VAS at different time points among the included RCTs. Therefore, future studies regarding chewing gum should investigate the intensity of pain at similar and multiple time points. In addition, the results of the Cochrane risk of bias tool revealed a high risk of bias among the studies included, and the quality of evidence across the studies was graded according to the results of GRADE approach to be a very low quality of evidence, which belongs to the GRADE's category stating that "we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect."

CONCLUSIONS

- In patients undergoing fixed orthodontic therapy, chewing gum is an effective intervention for reducing orthodontic pain after 24 hours of initial wire placement.
- Chewing gum may be considered a good substitute for pharmacologic interventions during fixed orthodontic treatment.
- The results of the GRADE approach revealed a very low quality of evidence across the studies included and emphasized the need for better quality RCTs regarding the role of chewing gum in reducing orthodontic pain so that future practice can be based on scientific evidence.

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