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Network Meta-Analysis
Temporomandibular Disorders

Effectiveness of occlusal splint therapy in the management of temporomandibular disorders: network meta-analysis of randomized controlled trials

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Abstract. A network meta-analysis (NMA) of randomized controlled trials (RCTs) was performed to assess the effectiveness of various types of occlusal splint in the management of temporomandibular disorders (TMDs) and to rank them according to their effectiveness. An electronic search was undertaken to identify RCTs published until August 2019. Predictor variables were control, non-occluding splint, hard stabilization splint (HSS), soft stabilization splint (SSS), prefabricated splint, mini-anterior splint, anterior repositioning splint (ARS), and counselling therapy (CT) with or without HSS. Outcome variables were pain improvement, post-treatment pain intensity, improvement in mouth opening, and disappearance of temporomandibular joint (TMJ) sounds. Forty-eight RCTs were included. There was a significant decrease in post-treatment pain intensity in arthrogenous TMDs after ARS (low quality evidence), CT + HSS (moderate quality evidence), mini-anterior splints (very low quality evidence), and HSS alone (low quality evidence), when compared to the control. There was a significant decrease in post-treatment pain intensity in myogenous TMDs with mini-anterior splints (very low quality evidence), SSS (very low quality evidence), CT alone (moderate quality evidence), CT + HSS (moderate quality evidence), and HSS alone (moderate quality evidence), when compared to control. ARS and CT were superior in decreasing TMJ clicking than control and HSS alone. The three highest-ranked treatments for post-treatment pain reduction in arthrogenous TMDs were ARS (92%, very low quality evidence), CT + HSS (67.3%, low quality evidence), and HSS alone (52.9%, moderate quality evidence). For myogenous TMDs, they were mini-anterior splints (86.8%, low quality evidence), CT + HSS (61.2%, very low quality evidence), and

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HSS alone (59.7%, moderate quality evidence). Based on this NMA of 48 RCTs, there is moderate to very low quality evidence confirming the effectiveness of occlusal splint therapy in the treatment of TMDs. Multimodal therapy consisting of CT + HSS may produce the maximum improvement for TMD patients.

Key words: arthrogenous temporomandibular disorders; myogenous temporomandibular disorders; network meta-analysis; randomized controlled clinical trials; TMJ clicking; occlusal splint therapy; hard stabilization splint; anterior repositioning splint; NTI-tss; counselling therapy; self-management; non-occluding splint.

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Temporomandibular disorders (TMDs) are classified into three categories based on their origin: myogenous, arthrogenous, and mixed[1,2]. Several predictable treatment modalities for TMDs of any origin have been documented, such as occlusal splints, counselling therapy, physiotherapy, oral or injectable pharmacotherapy, and arthrocentesis or arthroscopy[3].

A variety of occlusal splints for the treatment of TMDs have been reported in the literature. The most widely used splints are stabilization splints (Tanner appliance, Fox appliance, Michigan splint, or centric relation appliance), anterior repositioning splint, and anterior bite splint.

Several published systematic reviews have shown the efficacy of occlusal splints in the treatment of TMDs[3–8]. However, none of these systematic reviews has specifically covered randomized controlled clinical trials (RCTs) comparing the effectiveness of different occlusal splints versus control, non-occluding splints, or any of the other treatment modalities for myogenous, arthrogenous, or mixed TMDs. Furthermore, the effect of splint-wearing time and the total duration of occlusal splint therapy on the outcome of the treatment has not been investigated using a meta-analysis of RCTs with the GRADE system to rate the confidence of the evidence.

There are currently no published RCTs comparing the following different occlusal splints with or without counselling therapy and self-management in the management of TMDs: (1) full hard stabilization splint alone versus counselling in combination with a hard stabilization splint for patients with myogenous and arthrogenous TMDs; (2) non-occluding splints versus control, counselling with or without a hard stabilization splint, anterior repositioning splint, prefabricated splint, or nociceptive trigeminal inhibition tension suppression system (NTI-tss) in patients with mainly arthrogenous TMDs; (3) anterior repositioning splint versus full soft stabilization splint or a combination of full hard stabilization splint with counselling in patients with mainly arthrogenous TMDs; (4) mini-anterior splints such as the NTI-tss or midline anterior stop device versus the prefabricated splint or counselling plus full hard stabilization splint for patients with myogenous TMDs; (5) full soft stabilization splint alone versus NTI-tss, prefabricated splint, counselling with and without full hard stabilization splint, or full hard stabilization splint alone in patients with mainly myogenous TMDs. Therefore, a network meta-analysis (NMA) of RCTs was conducted to make comparisons among the different occlusal splints and counselling with and without a hard stabilization splint in order to rank the ideal and most effective occlusal splint in reducing signs and symptoms of TMDs.

The following hypotheses were considered in this analysis: (1) There would be no difference between a flat hard stabilization splint and other occlusal splints or counselling with or without a hard stabilization splint in the treatment of the signs and symptoms of TMDs. (2) Only patients with myogenous TMDs would significantly benefit from a hard stabilization splint compared to patients with arthrogenous or mixed TMDs. (3) There is no relationship between the duration of hard stabilization splint wearing and the type of TMD based on origin or the duration of follow-up with regard to splint efficacy.

The specific aims of this study were (1) to compare and rank the full hard stabilization splint, full soft stabilization splint, non-occluding splint, mini-anterior splint, prefabricated splint, anterior repositioning splint, and counselling therapy with and without a hard stabilization splint in the management of myogenous, arthrogenous, and mixed TMDs, with respect to pain reduction, mouth opening, and temporomandibular joint (TMJ) clicking; (2) to identify the effect of splint wearing time on its efficacy in pain reduction for patients with TMDs; (3) to assess the association between the duration of follow-up and the effectiveness of the hard stabilization splint.

Materials and methods

Protocol and registration

This study was accomplished according to the PRISMA extension statement for NMA[9] (**Supplementary Material** File 1). This study was registered in the PROSPERO database (CRD42018109352)[10].

Focused question

The following clinical research questions were established: (1) Does occlusal splint therapy treat TMDs? (2) What is the most effective oral occlusal splint for reducing pain intensity and TMJ clicking, and improving mouth opening for patients with arthrogenous and myogenous TMDs? (3) Does the pattern of hard stabilization splint wearing time have an impact on its efficacy in the treatment of TMDs?

Search strategy

All pertinent articles published between 1977 and March 2019 were identified through an electronic search of three major databases using the PICOTS criteria (**Supplementary Material** File 2).

Inclusion criteria

The PICOTS criteria were applied, as outlined below.

'P' (population): adult patients with pain due to myogenous, arthrogenous, or mixed TMDs (Ia and Ib). The diagnosis had to be based on the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) protocol, or a clear clinical diagnosis including signs and symptoms of TMDs.

'I' (intervention): different treatments for TMDs affecting the muscle, joint, or both using one of the following treatment modalities: (1) anterior repositioning splint (including maxillary or mandibular full coverage occlusal splints with an anterior ramp); (2) partial coverage splint such as an anterior midline stop device or the NTI-tss (including prefabricated or

custom-made hard splints covering the two maxillary or mandibular central incisors); (3) prefabricated splint (including those covering the edges of the incisors and canines and with a palatal extension of approximately 1 cm); (4) non-occluding splint (including passive non-occluding splints); (5) full-coverage soft or resilience stabilization splint (including full maxillary or mandibular coverage soft stabilization splints); (6) control/no treatment (including patients who did not receive any treatment or those on a waiting list for treatment); (7) counselling therapy and self-management according to the definitions of the behaviour change technique taxonomy (version 1)[11] (including basic elements of cognitive-behavioural therapy such as education, relaxation techniques, home physiotherapy (muscles exercises and joint mobilization), and avoidance of parafunctional habits); (8) counselling therapy plus hard stabilization splint (including any form of counselling therapy plus a full hard stabilization splint).

'C' (comparator): flat stabilization splint (including full hard maxillary or mandibular stabilization splints such as the Tanner appliance, Fox appliance, Michigan splint, or centric relation appliance).

'O' (outcomes): the primary outcome was pain intensity according to self-reported data (dichotomous data) or assessed clinically (continuous data) via visual analogue scale (VAS), numerical pain scale, or pain severity scale. Secondary outcomes were masticatory muscle tenderness (via algometer) and maximum mouth opening (MMO) in millimetres.

'T' (time): all included studies had to have followed up the patients for at least 1 month after treatment.

'S' (study design): RCTs comparing any occlusal splint to other treatments for patients with TMDs.

Exclusion criteria

The following studies were excluded: (1) non-randomized controlled clinical studies, (2) retrospective studies, (3) trials that did not investigate the outcomes of interest, (4) RCTs that did not report the required data as the mean and standard deviation values, as required to perform a meta-analysis, (5) RCTs that studied myofascial pain without clearly implicating the masticatory muscles.

Data extraction

Data were extracted separately by two researchers (R.F. and M.A.) using a specific form to summarize the following details: authors, study design, subgroup diagnosis, TMD diagnostic criteria used, age of the patients, male to female ratio, treatment groups (number), duration/frequency of treatment, outcomes investigated, and follow-up time.

Risk of bias

Two authors (R.F. and M.A.) investigated the risk of bias of included trials independently using the modified version of the Cochrane tool[12]. Any dispute between the two authors was resolved by a third reviewer (E.A.).

Data synthesis

For continuous data, the post-treatment value was used to compute the standardized mean difference (SMD). For dichotomous data, the risk ratio (RR) was analysed using the number of patients reporting an improvement in TMJ pain and associated masticatory muscles at a post-treatment time. All NMAs were conducted using a frequentist framework via random-effects model in Stata Release 13, 2013 (StataCorp LLC, College Station, TX, USA)[13] and the mvmeta command[14].

The loop-specific approach using the ifplot command in Stata and 'design-by-treatment' model using the mvmeta command were performed[14,15] to evaluate the assumption of consistency at the local and global levels. Additionally, the authors assumed a common heterogeneity estimate within each loop[14]. The ranking probabilities for all treatments at each possible rank for each group were analysed using the surface under the cumulative ranking (SUCRA) curve[16]. SUCRA can also be presented as a percentage of treatment that

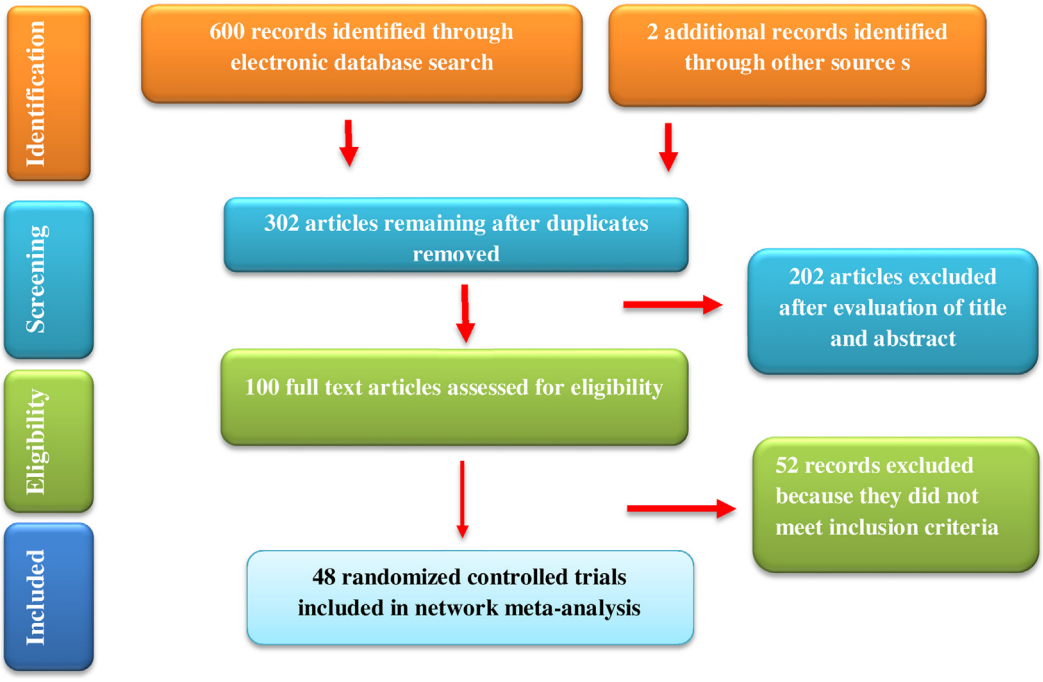

Fig. 1. PRISMA flow diagram.

can be ranked first without uncertainty. The rank-heat plot to visualize and present the treatment hierarchy across the multiple outcomes of interest was produced[16,17]. Subgroup analyses were performed according to (1) the origin of the TMD (myogenous, arthrogenous, or mixed); (2) the duration of follow-up, either short-term (≤6 months) or intermediate-term (>6 months); (3) the wearing time of the splints, either at night only or 24 hours a day.

Certainty of the evidence

The GRADE (Grading of Recommendations Assessment, Development and Evaluations) approach to meta-analysis was used to assess the certainty of the NMA effect estimates for all outcomes of interest[17,18]. In the GRADE system, RCTs begin as high quality evidence, but may be rated down due to limitations in the study design, inconsistency, imprecision, indirectness, and publication bias. The summary of confidence for the present evidence was estimated using the GRADEpro Guideline Development Tool[19,20].

Results

Outcome of the literature search

Of a total of 600 reports identified in all databases and two additional articles retrieved through the manual search, only 48 RCTs met the inclusion criteria and were included in the NMA[21–68]. Fig. 1 illustrates the process of article evaluation for inclusion in the systematic review and meta-analysis.

Presentation and summary of network geometry

With regard to the dichotomous data, 16 RCTs assessed the improvement in pain in 744 patients who received nine different treatments for TMDs of mainly arthrogenous origin (10 RCTs on arthrogenous TMDs; 6 RCTs on mixed TMDs) and 19 RCTs measured the improvement in pain in 946 patients who received eight different treatments for TMDs of mainly myogenous origin (13 RCTs on myogenous TMDs; 6 RCTs on mixed TMDs).

Regarding the continuous data, 16 RCTs evaluated post-treatment pain intensity in 929 patients who received eight different treatments for TMDs of mainly arthrogenous origin (9 RCTs on arthrogenous TMDs; 7 RCTs on mixed TMDs)

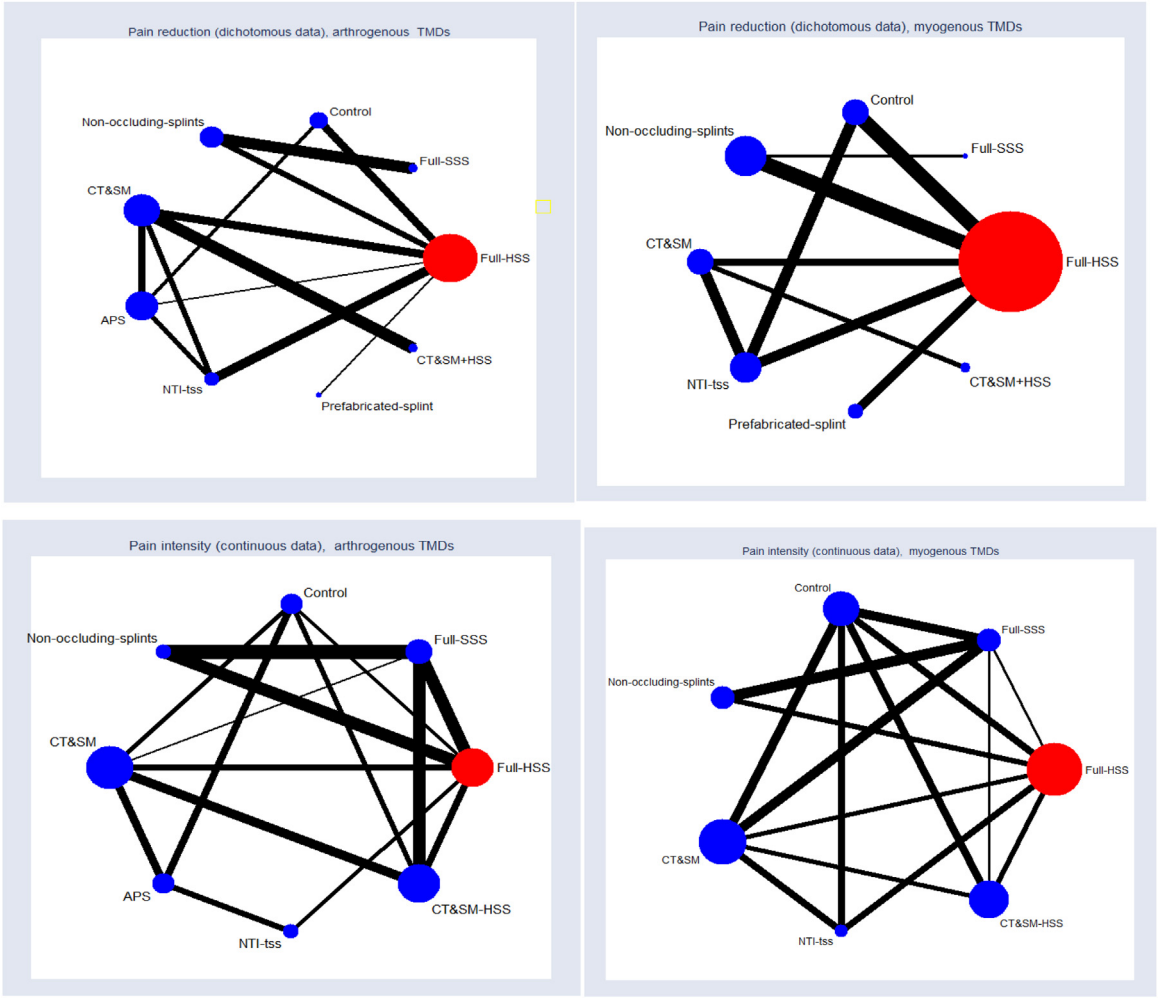

Fig. 2. Network geometry for the outcome of pain improvement (dichotomous data) and post-treatment pain intensity (continuous data) for arthrogenous and myogenous temporomandibular disorders. (Abbreviations: TMD, temporomandibular disorder; SSS, soft stabilization splint; HSS, hard stabilization splint; CT&SM, counselling therapy and self-management; NTI-tss, nociceptive trigeminal inhibition tension suppression system; ARS, anterior repositioning splint.)

and 18 RCTs measured post-treatment pain intensity in 1129 patients who received seven different treatments for TMDs of mainly myogenous origin (11 RCTs on myogenous TMDs; 7 RCTs on mixed TMDs) (Fig. 2).

Features of included trials

A full description of the trials, patient age and sex distribution, and how the treatments were conducted in all groups is given in **Supplementary Material** File 3.

Risk of bias

Twenty-five RCTs had an unclear risk of bias[21–30,34–36,45,46,48,49,51,53,56,62,63,64,67,68], 13 RCTs had a low risk of bias[31,33,37,38,43,50,52,54,57,59,60,61,66], and 10 RCTs had a high risk of bias[32,39–42,44,47,55,58,65]. Allocation concealment was adequate in 27 RCTs[22,24–26,30,31,33,35,37,38,40,42–45,50,52,54,55,57–62,64,66]. Assessment of outcome assessors showed that 24 RCTs were assessed by a blinded assessor[22,24,31,33,34,37–39,41,43,45,47,48,50,52–55,57,59–61,64,66], four RCTs were not blinded[32,40,42,44], and 20 RCTs did not report any information about blinding of assessors[21,23,25–30,35,36,46,49,51,56,58,62,63,65,67,68]. Nine RCTs had an attrition bias[23,27,29,30,44,50,55,58,65], 17 RCTs had no attrition bias[26,31,33,35,37,38,43,47,49,52,54,57,59,60,61,66,67], and 22 RCTs did not report any information about dropouts[21,22,24,25,28,32,34,36,39–42,45,46,48,51,53,56,62,63,64,68] (**Supplementary Material** File 4).

Results of individual studies

Online **Supplementary Material** File 5 summarizes the details of the outcomes. For dichotomous data, the number of patients reporting an improvement in pain and TMJ clicking and the total number of patients are stated. For continuous data, the mean, standard deviation, and sample size for the outcome of pain intensity and MMO are reported.

Synthesis of results—Results of the outcome variables

Pain improvement (dichotomous data): number of patients reporting pain improvement in RCTs including patients with TMDs of mainly arthrogenous origin (risk ratio)

Sixteen RCTs evaluated changes in pain reduction in 744 patients who received different treatments for TMDs of mainly arthrogenous origin (10 RCTs on arthrogenous TMDs; 6 RCTs on mixed TMDs)[21,22,24,28,33,34,36,39,48,53,54,55,58,59,61,64]. The follow-up time ranged from 1 to 12 months. There was no significant difference in pain improvement between the hard stabilization splint and the other treatments (Fig. 3).

Pain improvement (dichotomous data): number of patients reporting pain improvement in RCTs including patients with TMDs of mainly myogenous origin (risk ratio)

Nineteen RCTs assessed pain intensity in 946 patients who received different treatments for TMDs of mainly myogenous origin (13 RCTs on myogenous TMDs; 6 RCTs on mixed TMDs)[23,25,26,30,32,34,38,39,40,46,51,54,55,56,57,58,59,60,64]. The follow-up time ranged from 1 month to 12 months.

There was a significant pain reduction after hard stabilization splint compared to control (RR 0.46, 95% confidence interval (CI) 0.26–0.80; low quality evidence) and non-occluding splints (RR 0.58, 95% CI 0.41–0.83; moderate quality evidence) (Fig. 4).

A significant pain reduction was noted with the use of hard stabilization splints (RR 2.18, 95% CI 1.25–3.8; moderate quality evidence), prefabricated splints (RR 2.24, 95% CI 1.12–4.49; very low quality evidence), and NTI-tss splints (RR 0.2.41, 95% CI 1.26–4.60; low quality evidence) when compared to control.

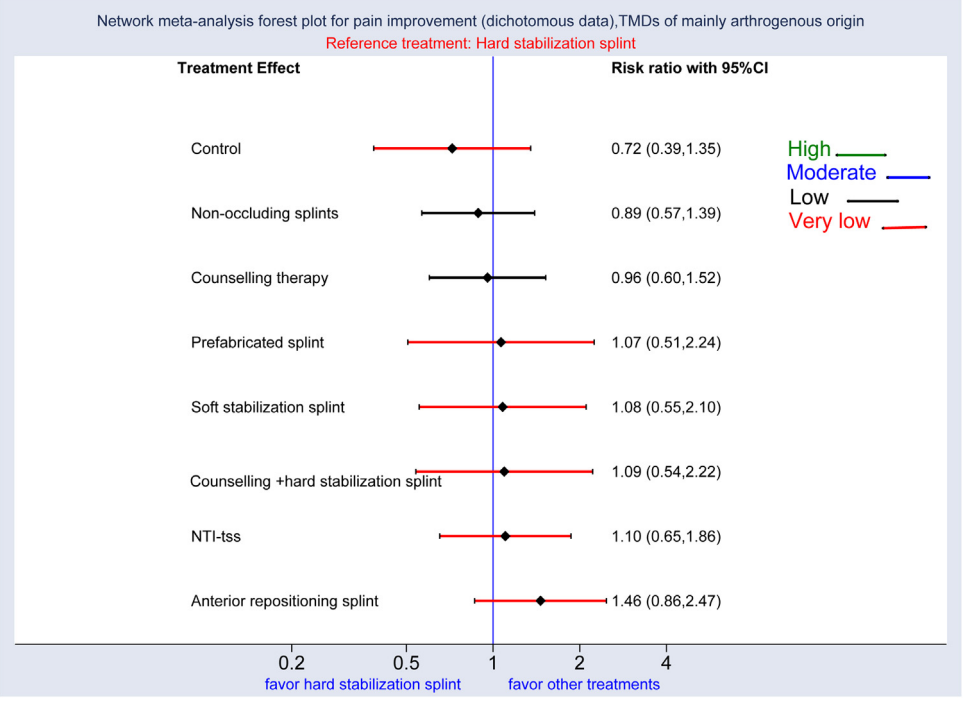

Fig. 3. Network meta-analysis forest plot for pain improvement (dichotomous data): the number of patients reporting pain improvement in RCTs including patients with TMDs of mainly arthrogenous origin. (Abbreviations: RCT, randomized controlled trial; TMD, temporomandibular disorder; RR, risk ratio; CI, confidence interval; PrI, prediction interval; NTI-tss, nociceptive trigeminal inhibition tension suppression system.)

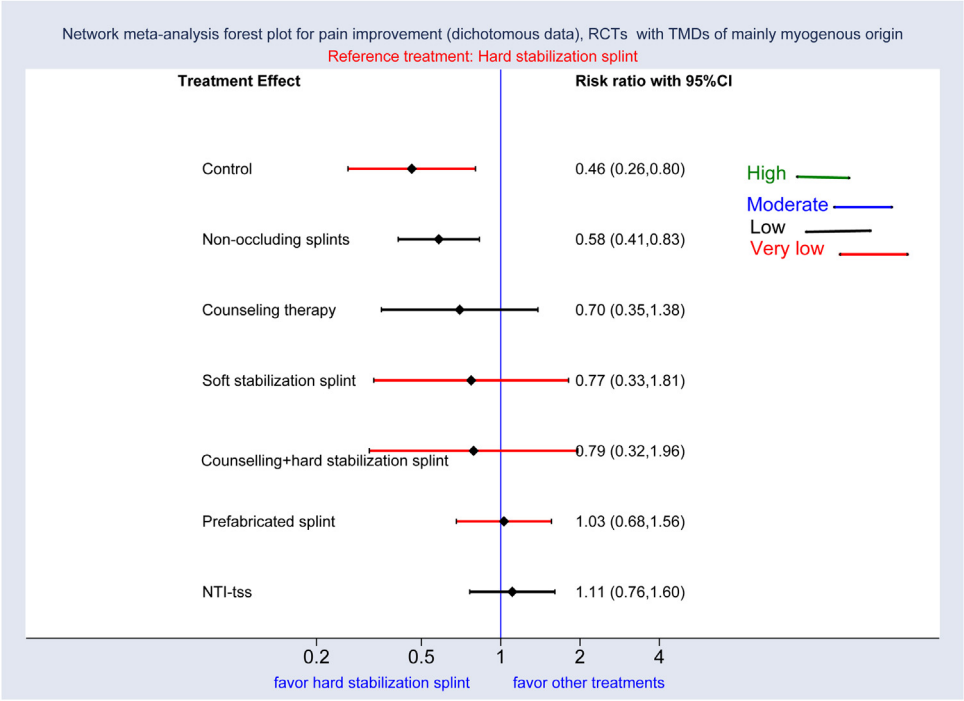

Fig. 4. Network meta-analysis forest plot for pain improvement (dichotomous data): the number of patients reporting pain improvement in RCTs including patients with TMDs of mainly myogenous origin. (Abbreviations: RCT, randomized controlled trial; TMD, temporomandibular disorder; RR, risk ratio; CI, confidence interval; PrI, prediction interval; NTI-tss, nociceptive trigeminal inhibition tension suppression system.)

Hard S splint	−0.04 (−0.45,0.38)	−0.27 (−1.01,0.47)	−0.44 (−1.13,0.26)	0.20 (−0.21,0.60)	0.31 (−0.33,0.95)	**0.74 (0.11,1.38)**	0.32 (−0.24,0.87)
0.04 (−0.38,0.45)	**CT + hard splint**	−0.24 (−1.04,0.57)	−0.40 (−1.13,0.32)	0.23 (−0.14,0.60)	0.35 (−0.35,1.05)	**0.78 (0.14,1.42)**	0.35 (−0.23,0.94)
0.27 (−0.47,1.01)	0.24 (−0.57,1.04)	**Mini-anterior splints**	−0.17 (−0.83,0.50)	0.47 (−0.31,1.25)	0.58 (−0.38,1.55)	**1.02 (0.17,1.87)**	0.59 (−0.31,1.49)
0.44 (−0.26,1.13)	0.40 (−0.32,1.13)	0.17 (−0.50,0.83)	**Anterior R splint**	0.64 (−0.04,1.31)	0.75 (−0.17,1.66)	**1.18 (0.47,1.90)**	0.75 (−0.09,1.59)
−0.20 (−0.60,0.21)	−0.23 (−0.60,0.14)	−0.47 (−1.25,0.31)	−0.64 (−1.31,0.04)	**CT**	0.11 (−0.58,0.81)	0.55 (−0.08,1.17)	0.12 (−0.46,0.69)
−0.31 (−0.95,0.33)	−0.35 (−1.05,0.35)	−0.58 (−1.55,0.38)	−0.75 (−1.66,0.17)	−0.11 (−0.81,0.58)	**Non-occluding splints**	0.43 (−0.43,1.30)	0.00 (−0.56,0.57)
−0.74 (−1.38,−0.11)	**−0.78 (−1.42,−0.14)**	**−1.02 (−1.87,−0.17)**	**−1.18 (−1.90,−0.47)**	−0.55 (−1.17,0.08)	−0.43 (−1.30,0.43)	**Control**	−0.43 (−1.21,0.36)
−0.32 (−0.87,0.24)	−0.35 (−0.94,0.23)	−0.59 (−1.49,0.31)	−0.75 (−1.59,0.09)	−0.12 (−0.69,0.46)	−0.00 (−0.57,0.56)	0.43 (−0.36,1.21)	**Soft S splint**

Fig. 5. Network meta-analysis net league for post-treatment pain intensity (continuous data); RCTs including patients with TMDs of mainly arthrogenous origin (SMD, standardized mean difference).
An SMD of less than 0 favours the treatments in the column; an SMD of more than 0 favours the treatments in the row. Numbers in bold represent statistically significant results. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. (Abbreviations: S, stabilization; CT, counselling therapy; R, repositioning.)

Post-treatment pain intensity (continuous data): RCTs including patients with TMDs of mainly arthrogenous origin (SMD)

Sixteen RCTs evaluated pain intensity in 929 patients who received different treatments for TMDs of mainly arthrogenous origin (9 RCTs on arthrogenous TMDs; 7 RCTs on mixed TMDs)[36,37,44,45,47,49,50,52,53,54,55,58,59,62,64,66]. The follow-up time ranged from to 1 to 12 months post-treatment.

There was a significant decrease in post-treatment pain intensity following hard stabilization splint (SMD −0.74, 95% CI −1.38 to −0.11; low quality evidence), anterior repositioning splint (SMD −1.18, 95% CI −1.90 to −0.47; low quality evidence), counselling therapy plus hard stabilization splint (SMD −0.78, 95% CI −1.42 to −0.14; moderate quality evidence), and mini-anterior splints (SMD −1.02, 95% CI −1.87 to −0.17; very low quality evidence) when compared to control (Fig. 5).

Post-treatment pain intensity (continuous data): RCTs including patients with TMDs of mainly myogenous origin (SMD)

Eighteen RCTs measured pain intensity in 1129 patients who received different treatments for TMDs of mainly myogenous origin (11 RCTs on myogenous TMDs; 7 RCTs on mixed TMDs)[27,29,31,35,38,41,42,44,46,47,54,58,59,60,62,63,64,68]. The follow-up time ranged from to 1 to 12 months.

There was a significant decrease in post-treatment pain intensity following hard stabilization splint (SMD −1.25, 95% CI −1.69 to −0.80; moderate quality evidence), NTI-tss (SMD −1.49, 95% CI −2.19 to −0.79; very low quality evidence), soft stabilization splint (SMD −1.23, 95% CI −1.86 to −0.61; very low quality evidence), counselling therapy (SMD −1.04, 95% CI −1.55 to −0.52; moderate quality evidence), and counselling therapy plus hard stabilization splint (SMD −1.18, 95% CI −1.72

Hard S splint	0.07 (−0.36,0.49)	−0.24 (−0.91,0.42)	0.21 (−0.21,0.62)	0.26 (−0.18,0.69)	**1.25 (0.80,1.69)**	0.01 (−0.50,0.53)
−0.07 (−0.49,0.36)	**CT + hard splint**	−0.31 (−1.02,0.40)	**0.14 (−0.20,0.49)**	0.19 (−0.38,0.77)	**1.18 (0.64,1.72)**	−0.05 (−0.62,0.52)
0.24 (−0.42,0.91)	0.31 (−0.40,1.02)	**Mini-anterior splints**	0.45 (−0.21,1.12)	0.50 (−0.28,1.28)	**1.49 (0.79,2.19)**	0.26 (−0.54,1.06)
−0.21 (−0.62,0.21)	−0.14 (−0.49,0.20)	−0.45 (−1.12,0.21)	**CT + self-care**	0.05 (−0.52,0.62)	**1.04 (0.52,1.55)**	−0.20 (−0.77,0.38)
−0.26 (−0.69,0.18)	−0.19 (−0.77,0.38)	−0.50 (−1.28,0.28)	−0.05 (−0.62,0.52)	**Non-occluding splints**	**0.99 (0.38,1.59)**	−0.25 (−0.76,0.27)
−1.25 (−1.69,−0.80)	**−1.18 (−1.72,−0.64)**	**−1.49 (−2.19,−0.79)**	**−1.04 (−1.55,−0.52)**	**−0.99 (−1.59,−0.38)**	**Control**	**−1.23 (−1.86,−0.61)**
−0.01 (−0.53,0.50)	0.05 (−0.52,0.62)	−0.26 (−1.06,0.54)	0.20 (−0.38,0.77)	0.25 (−0.27,0.76)	**1.23 (0.61,1.86)**	**Soft S splint**

Fig. 6. Network meta-analysis net league for post-treatment pain intensity (continuous data); RCTs including patients with TMDs of mainly myogenous origin (SMD, standardized mean difference).
An SMD of less than 0 favours the treatments in the column; an SMD of more than 0 favours the treatments in the row. Numbers in bold represent statistically significant results. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. (Abbreviations: S, stabilization; CT, counselling therapy.)

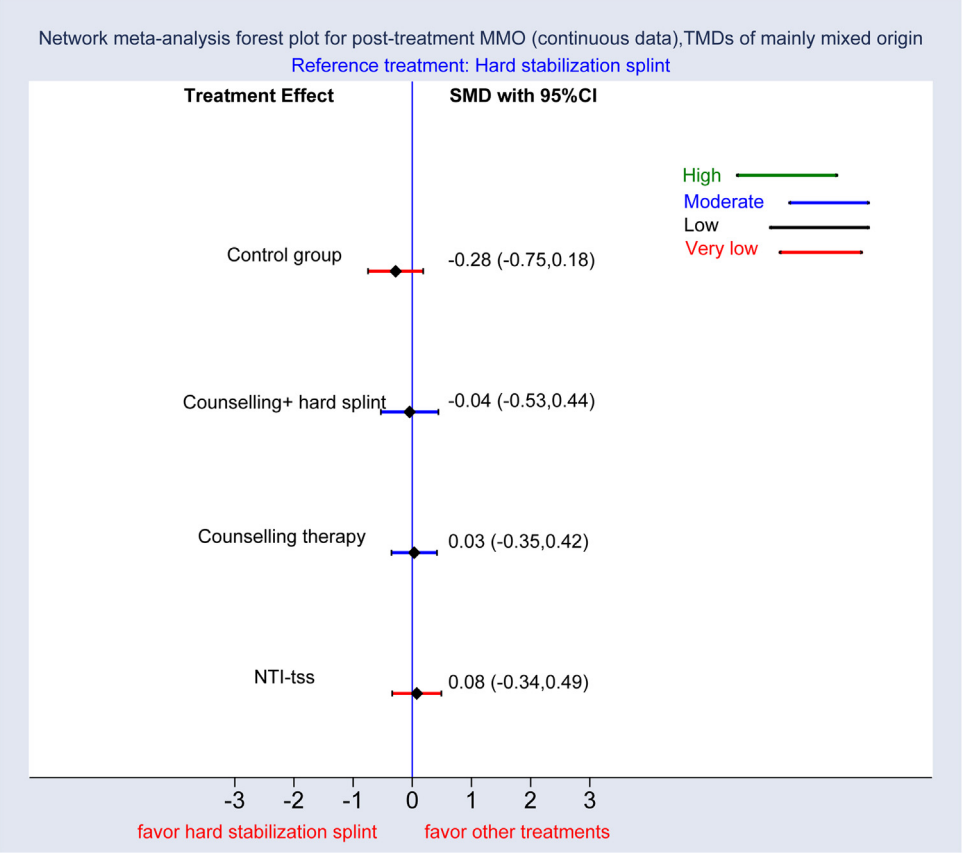

Fig. 7. Network meta-analysis forest plot for post-treatment MMO (continuous data): RCTs including patients with TMDs of mainly mixed origin. (Abbreviations: MMO, maximum mouth opening; RCT, randomized controlled trial; TMD, temporomandibular disorder; SMD, standardized mean difference; CI, confidence interval; PrI, prediction interval; NTI-tss, nociceptive trigeminal inhibition tension suppression system.)

to −0.64; moderate quality evidence) when compared to control (Fig. 6).

Post-treatment MMO: RCTs including patients with arthrogenous and myogenous TMDs (SMD)

Twelve RCTs measured the improvement in MMO in 491 patients who received different treatments for TMDs of arthrogenous and myogenous origin (8 RCTs on arthrogenous TMDs; 2 RCTs on myogenous TMDs; 2 RCTs on mixed TMDs)[31,35,36,37,45,50,52,55,58,61,62,66]. The predictor variables were control group, counselling therapy, counselling therapy plus hard stabilization splint, and partial coverage splints such as NTI-tss and prefabricated splints. The follow-up time ranged from 1 to 12 months. There was no significant difference for any comparison (Fig. 7).

Improvement in TMJ clicking: number of patients reporting the disappearance of TMJ clicking in RCTs including patients with mainly arthrogenous TMDs (risk ratio)

Thirteen RCTs recorded improvements in TMJ clicking in 789 patients who received treatment for TMDs of mainly arthrogenous origin (2 RCTs on myogenous TMDs; 2

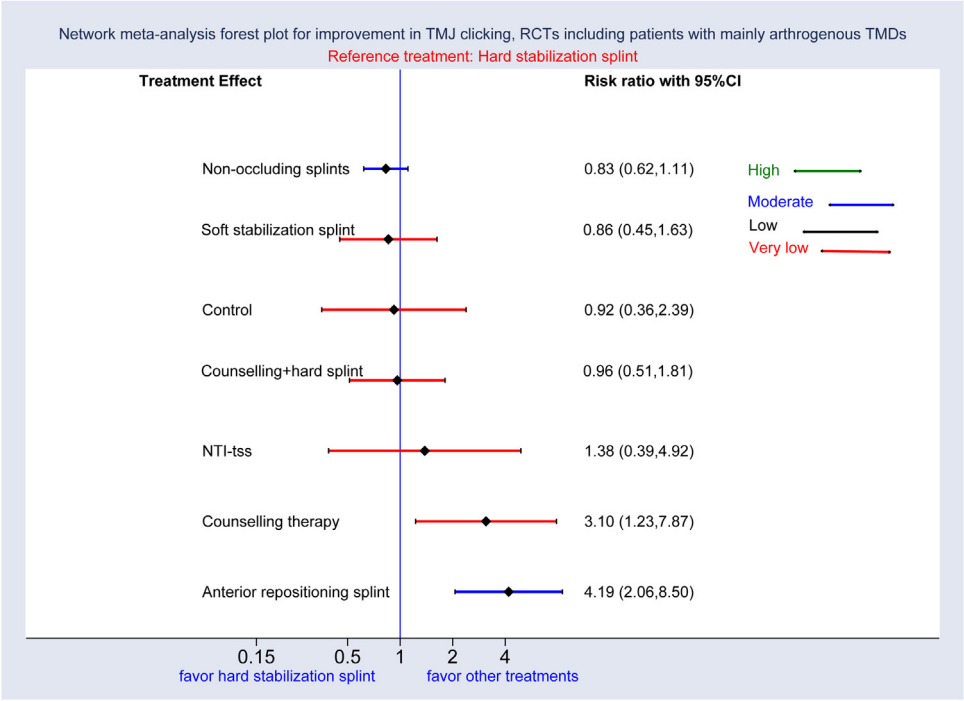

Fig. 8. Network meta-analysis forest plot for improvement in TMJ clicking: the number of patients reporting the disappearance of TMJ clicking in RCTs including patients with mainly arthrogenous TMDs. (Abbreviations: TMJ, temporomandibular joint; RCT, randomized controlled trial; TMD, temporomandibular disorder; CI, confidence interval; PrI, prediction interval; NTI-tss, nociceptive trigeminal inhibition tension suppression system.)

RCTs on mixed TMDs; 9 RCTs on arthrogenous TMDs)[21,22,24,33,39,42,43,44,47,48,49,53,55].

There was significantly decreased TMJ clicking after anterior repositioning splint (RR 4.19, 95% CI 2.06–8.50; moderate quality evidence) and counselling therapy (RR 3.10, 95% CI 1.23–7.87; very low quality evidence) when compared to hard stabilization splint (Fig. 8).

There was a significant decrease in TMJ sounds following anterior repositioning splint (RR 4.54, 95% CI 2.17–9.50; moderate quality evidence) and counselling therapy (RR 3.37, 95% CI 1.33–8.52; moderate quality evidence) versus control.

Synthesis of results—Treatment ranking

Pain reduction for patients with TMDs of mainly arthrogenous origin

From the dichotomous data, the most effective treatment to reduce pain in patients with TMDs of arthrogenous origin at follow-up ranging from 1 to 12 months was anterior repositioning splint (86.5%, very low quality evidence), followed by counselling therapy and self-management plus hard stabilization splint (75.6%, very low quality evidence), NTI-tss (58%, very low quality evidence), soft stabilization splint (56.3%, very low quality evidence), prefabricated splint (53.3%, very low quality evidence), hard stabilization splint (47.5%, moderate quality evidence), counselling therapy and self-management (40.8%, low quality evidence), non-occluding splints (32.4%, low quality evidence), and control (17.5%, very low quality evidence) (Fig. 9 and **Supplementary Material** File 6).

From the continuous data, the ranking of effectiveness of treatment in reducing pain in patients with TMDs at follow-up ranging from 1 to 12 months was anterior repositioning splint (92%, very low quality evidence), NTI-tss (76.9%, very low quality evidence), counselling therapy plus hard stabilization splint (67.3%, low quality evidence), hard stabilization splint (52.9%, moderate quality evidence), counselling therapy (48%, moderate quality evidence), soft stabilization splint (29.3%, very low quality evidence), non-occluding splints (28.3%, very low quality evidence), and control (5.2%, very low quality evidence) (Fig. 10 and **Supplementary Material** File 6).

Pain reduction for patients with TMDs of mainly myogenous origin

From the dichotomous data, the most effective treatment to reduce pain in patients with TMDs at follow-up ranging from 1 to 12 months was NTI-tss (81.3%, low quality evidence), followed by prefabricated splint (74.4%, very low quality evidence), hard stabilization splint (71.8%, moderate quality evidence), counselling therapy plus hard stabilization splint (50.6%, very low quality evidence), soft stabilization splint (49.4%, very low quality evidence), counselling therapy (38.7%, low quality evidence), non-occluding splints (23.5%, very low quality evidence), and control (10.4%, very low quality evidence) (Fig. 9 and **Supplementary Material** File 6).

From the continuous data, the most effective treatment to reduce pain in patients with TMDs at follow-up ranging from 1 to 12 months was NTI-tss (86.8%, low quality evidence), followed by soft stabilization splint (61.9%, very low quality evidence), counselling therapy plus hard stabilization splint (61.2%, very low quality evidence), hard stabilization splint (59.7%, moderate quality evidence), counselling therapy (50.8%, low quality evidence), non-occluding splints (29.8%, very low quality evidence), and control (0%, very low quality evidence) (Fig. 10 and **Supplementary Material** File 6).

MMO in patients with arthrogenous and myogenous TMDs (continuous data only)

The most effective treatment to improve mouth opening in patients with TMDs

Fig. 9. Rank-heat plot identifying a hierarchy of multiple treatments for all dichotomous outcomes. (Abbreviations: HSS, hard stabilization splint; SSS, soft stabilization splint; NTI-tss, nociceptive trigeminal inhibition tension suppression system; ARS, anterior repositioning splint; CT&SM, counselling therapy and self-management; ARG, arthrogenous; MYG, myogenous; TMJ, temporomandibular joint.)

affecting the TMJ and masticatory muscles at follow-up ranging from 1 to 12 months was mini-anterior splints (67.9%, very low quality evidence), followed by counselling therapy (63.7%, moderate quality evidence), hard stabilization splint (56.2%, moderate quality evidence), counselling therapy plus hard stabilization splint (48.2%, moderate quality evidence), and control (14%, very low quality evidence) (Fig. 10 and **Supplementary Material** File 6).

TMJ clicking in patients with mainly arthrogenous TMDs (dichotomous data)

The most effective treatment to decrease TMJ clicking in patients with TMDs affecting the TMJ and masticatory muscles at follow-up ranging from 1 to 12 months was anterior repositioning splint (98.3%, moderate quality evidence), followed by counselling therapy (84.8%, very low quality evidence), NTI-tss (50.6%, very low quality evidence), hard stabilization splint (42%, moderate low quality evidence), control (40.7%, very low evidence), counselling therapy plus hard stabilization splint (37%, very low quality evidence), soft stabilization splint (26.7%, very low quality evidence), and non-occluding splint (20.6%, moderate quality evidence) (Fig. 9 and **Supplementary Material** File 6).

Additional analyses

Meta-regression analysis

In the analysis of pain improvement following full hard stabilization splint according to the type of TMD based on its origin (myogenous, arthrogenous, or mixed), there was a positive statistically significant association between pain reduction and the different diagnoses of TMD ($r = 13.08$, $P = 0.001$). There was an insignificant positive association between pain reduction and myogenous TMDs ($r = 2.77$, $P = 0.141$) and mixed TMDs ($r = 0.26$, $P = 0.920$); however, a negative association in patients with arthrogenous TMDs was found ($r = -3.39$, $P = 0.058$).

In the analysis of pain reduction following full hard stabilization splint according to the duration of follow-up (short-term and long-term), there was a positive association between pain reduction and short-term follow-up, but a negative association was found for long-term follow-up.

In the analysis of pain reduction following full hard stabilization splint according to splint usage time per day (at night or 24 hours per day), there was a significant pain reduction following wearing the hard stabilization splint at night when compared to wearing the hard stabilization splint 24 hours per day, regardless of the origin of the TMD or the duration of follow-up.

Sensitivity analysis

The NMA based on sensitivity analysis (after including RCTs that only involved either arthrogenous TMDs or myogenous TMDs and excluding RCTs involving subjects with both arthrogenous and myogenous TMDs simultaneously) showed no significant changes in pain reduction (dichotomous data) or post-treatment pain

Fig. 10. Rank-heat plot identifying a hierarchy of multiple treatments for all continuous outcomes. (Abbreviations: CT&SM, counselling therapy and self-management; ARS, anterior repositioning splint; SSS, soft stabilization splint; NTI-tss, nociceptive trigeminal inhibition tension suppression system; HSS, hard stabilization splint; ARG, arthrogenous; MYG, myogenous; MMO, maximum mouth opening.)

intensity (continuous data) among the results.

Publication bias

The publication bias for the dichotomous outcome of pain reduction is presented in **Supplementary Material** File 7. The funnel plot was almost symmetrical, showing that no publication bias was identified.

Exploration for inconsistency in NMA

For the dichotomous and continuous data based on the loop-specific test (for local inconsistency), there was no statistical inconsistency for all outcomes. Also, global inconsistency assumptions via design-by-treatment interaction models showed the absence of incoherence. Furthermore, all *P*-values for all outcomes were less than 0.05 (**Supplementary Material** File 8).

Confidence of evidence

The confidence of the evidence for all outcomes assessed in the current study ranged from moderate to very low quality evidence. Most of the certainties had lower confidence due to the risk of bias (lacking blinded assessors, attrition bias, and allocation concealment) and imprecision (due to small sample size and crossing the null hypothesis). Further details on the certainty of confidence for all outcomes are summarized in **Supplementary Material** File 9.

Discussion

The key findings of this study are the following: (1) there was a significant decrease in post-treatment pain intensity following full hard stabilization splint, anterior repositioning splint, counselling therapy plus hard stabilization splint, and NTI-tss when compared to control in patients with arthrogenous TMDs. (2) There was a significant decrease in post-treatment pain intensity after hard and soft stabilization splints, NTI-tss, and counselling therapy with/without a hard stabilization splint when compared to control in patients with myogenous TMDs. (3) Anterior repositioning splints and counselling therapy significantly lowered the incidence of TMJ clicking when compared to a full hard stabilization splint and control. (4) The most effective treatment to reduce pain in patients with mainly arthrogenous TMDs was anterior repositioning splint, followed by counselling therapy and self-management with hard stabilization splint. (5) The most effective treatment to reduce pain in patients with mainly myogenous TMDs was NTI-tss, followed by hard stabilization splint and counselling therapy plus hard stabilization splint. (6) The most effective treatment to improve mouth opening in patients with TMDs affecting the TMJ and masticatory muscles was anterior midline stop devices, followed by counselling therapy and hard

stabilization splint alone. (7) Subgroup analyses showed substantial pain reduction following full hard stabilization splint at short-term follow-up and with wearing the hard stabilization splint only at night, which is in contrast to long-term follow-up and with wearing the hard stabilization splint for 24 hours per day.

Control untreated patients

The NMA showed a significant pain reduction with the anterior repositioning splint when compared to control. A hard stabilization splint alone did not show any substantial difference from control. These comparable results for the elimination of TMJ pain for the hard stabilization splint and untreated control groups could be attributed to the continuation of the main cause of the TMJ pain, which is an abnormal relationship between the disc and condyle (disc displacement with/without reduction); a hard stabilization splint would not correct this abnormal relationship. On the other hand, the anterior repositioning splint is able to correct the position of the articular disc. Hence it has a superior pain reduction effect when compared to the untreated control.

Although hard stabilization splints showed a modest performance in treating arthrogenous TMDs, there was moderate quality evidence indicating that hard stabilization splints were superior to the control in treating patients with myogenous TMDs with regards to pain reduction and pain intensity. These results are in accordance with those of other previous studies[27,25,29,32,46,56,63,69,70].

Non-occluding splint

Based on the SUCRA ranking, which is a unique feature of the NMA, non-occluding splints ranked superior to control for arthrogenous and myogenous TMDs (non-occluding splints ranked seventh and control ranked eighth in last position). Those studies claimed that this result favouring non-occluding splints might be due to a positive placebo response, as well as the presence of the lingual flange, which affects tongue position and increases cognitive awareness of parafunctional habits[30,47,44]. This positive placebo effect cannot be overlooked, particularly in patients with myogenous TMDs. In summary, there was weak evidence supporting the efficacy of non-occluding splints in reducing pain in patients with arthrogenous TMDs.

For myogenous TMDs, the hard stabilization splint seems to be more effective than non-occluding splints in respect to pain improvement (moderate quality evidence). This result is similar to those of some studies[5,38,42,44]. However, the NMA showed no substantial difference between the hard stabilization splint and non-occluding splint (low quality evidence) in regards to post-treatment pain intensity, which is also similar to the findings of several other studies[4,30,44,54].

Soft stabilization splint

There was evidence of very low quality suggesting little difference between hard stabilization splints and soft stabilization splints in the improvement of pain and post-treatment pain intensity for patients with arthrogenous and myogenous TMDs. However, the soft stabilization splint ranked higher than the hard stabilization splint for the treatment of myogenous TMDs, but lower for arthrogenous TMDs when compared to hard stabilization splint. These results are in line with those of previous studies, indicating that the splint material has no impact on its effectiveness when used for masticatory TMDs[54,71,72].

Counselling therapy and self-management

A very low certainty of evidence suggests that counselling therapy significantly reduces TMJ sounds when compared to the hard stabilization splint and untreated control patients. Other studies have reported similar results[73–75]. A possible explanation for how muscle exercise and joint mobilization reduce TMJ sounds could be that disc capturing occurs during protrusive mandibular movements. This was confirmed in 23.1% of cases using MRI after therapeutic exercise in patients with reducible discs[67]. Also, the increased joint space during exercise allows easier and smoother condylar translation above the disc surface irregularities caused by the abnormal disc–condyle complex[67,75,76].

Counselling therapy yielded superior results for post-treatment pain intensity when compared to untreated control patients. This is in contrast to the conclusions of other studies[69,73,77].

The similarities in performance between counselling therapy and hard stabilization splint use support the postulati on that the beneficial effects of the hard stabilization splint in TMD patients result from a change in cognitive awareness rather than unloading of the TMJs. The results of the present study are in agreement with those of previously published studies[4,5,29,35,55].

Anterior repositioning splint

The positive effect of the anterior repositioning splint in the reduction of TMJ pain and sounds and improvement of mandibular function in patients with arthrogenous TMDs can be attributed either to the achievement of a normal disc–condyle relationship and the recapture of the displaced articular disc by anterior relocation of the condyle[24,78], or to making the displaced articular disc return backwards to its normal position in the therapeutic lower jaw position[39]. These recaptured discs are returned to their anterior locations after 6 months of wearing the anterior repositioning splint[78].

Although anterior repositioning splints seem to be superior to flat hard stabilization splints in reducing TMJ pain in patients with anterior disc displacement with reduction and arthralgia, the flat hard stabilization splint is still considered an effective option in the treatment of such patients[78–80]. Therefore, it has been recommended that dual splint therapy be used for the treatment of patients with arthrogenous TMDs. For patients with anterior disc displacement with reduction without a history of transient locking, the flat hard stabilization splint could be a reasonable primary option to eliminate TMJ pain and noises[81]. In the case of an intermediate stage of disc displacement starting from Wilkes type II patients with a history of transient locking, the initial recommended splint is an anterior repositioning splint for a short time (2–3 months), followed by a flat hard stabilization splint, or removal of the anterior ramp of the anterior repositioning splint[65,79]. Likewise, for patients with TMJ arthralgia, the anterior repositioning splint should be used for 2–3 months as an initial splint in those patients with acute severe joint inflammation, followed by a flat hard stabilization splint.

Mini-anterior splint (NTI-tss and anterior midline stop splint)

The results of this study are in accordance with those of previous studies in regard to mini-anterior splints[46,55,68,82]. However, another RCT showed that a full hard stabilization splint is superior to the NTI-tss[34]. The concept of the NTI-tss is based on disconnection of the posterior teeth, thus eliminating the excessive forces of posterior occlusion on the muscles of mastication, which in turn will protect

the teeth[83]. Additionally, the NTI-tss allows the repositioning of the condyle in a more posterosuperior position in those patients with an abnormal condylar position[65]. Due to its partial coverage, occlusal changes such as anterior bite (owing to either intrusion of the maxillary/mandibular teeth or overeruption of the posterior teeth) and traumatic mobility of the anterior teeth caused by occlusal forces have been reported[83,84]. Finally, because of its small design, it could be swallowed or aspirated, causing life-threating complications. There are five such recorded complications in the literature[84,85].

Prefabricated splint

The concept of the prefabricated splint conforms with partial coverage oral appliances, since the prefabricated splint covers six anterior teeth (incisors and canines) with about 1 cm palatal extension. Thus, both types of splint (NTI-tss and the prefabricated splint) have a similar mechanism of action. Therefore, the alleviation of signs and symptoms in patients with myogenous TMDs with the NTI-tss is not limited to this device. In other words, all partial coverage splints may produce effective results in pain reduction that are comparable to those of the traditional hard stabilization splint. However, only a limited number of RCTs were included in the current NMA: one RCT in arthrogenous TMDs[61] and two RCTs in myogenous TMDs[51,57].

Counselling therapy and self-management plus hard stabilization splint

An interesting finding of this study is that the supplementary treatment of counselling therapy with the hard stabilization splint had a minor additional advantage in patients with articular disc displacement when compared with use of the hard stabilization splint alone. This is in agreement with previous RCTs that have included patients with mixed TMDs[47,58,62,64]. However, RCTs that have recruited only patients with anterior disc displacement have shown that counselling therapy such as muscle exercise, joint mobilization, and self-management produce a positive outcome with or without a hard stabilization splint. This contradicts the findings of our study.

For myogenous TMDs, there was evidence ranging from very low to low quality suggesting that counselling therapy plus a hard stabilization splint does not add any advantages over hard stabilization splint alone in pain improvement, post-treatment pain intensity, and improved mouth opening. The results of other studies have shown similar findings[47,58,62,64,86]. Conti et al. reported that a combination of counselling therapy with a hard stabilization splint could produce earlier improvements for patients with myogenous TMDs as compared to the use of a hard stabilization splint alone[48]. The patients' initial improvement could explain the presence of insignificant additional benefits of the hard stabilization splint over counselling therapy in reducing the signs and symptoms of myogenous TMDs after counselling therapy, due to guidance, the natural course of the disease, avoiding parafunctional habits, or self-management resulting from cognitive and distraction therapy. Thus any further cognitive therapy such as a hard stabilization splint would not add any additional benefit[55,71].

The study results conform to the fact that counselling therapy has an earlier impact on the patients' subjective perception of pain as measured with a VAS[55,87].

Weaknesses and advantages of this study

This study has the following weaknesses: (1) the majority of included RCTs used the RDC/TMD as a diagnostic tool to select and recruit their patients. However, some RCTs used other criteria for clinical examination[21,22,23,24,26,29,31,32,33], particularly those RCTs published before 1992. (2) Blinding of both patients and researchers could not be performed because most of the interventions were occlusal splint devices. Hence masking of patients and investigators were eliminated from the assessment tool for the risk of bias. Furthermore, the primary outcome of the present study was pain, which depends on the patient's perception; hence, the elimination of performance bias could not be guaranteed. (3) The variation in chronicity and duration of the TMJ or muscular problems at the baseline level in the included RCTs may have caused inaccurate measurement of the outcomes of interest. (4) Inconsistencies in the duration of follow-up and diagnosis subsets of TMDs in the included RCTs may have affected the integrity of the results. So, meta-regression and subgroup analyses were done to assess the real impact of these effect modifiers. (5) Different tools were used to measure the outcome of pain, such as a VAS, numerical rating scale, characteristic pain intensity, and pain severity score. Thus, the SMD was used to analyse these outcomes, which were measured using different scales[12]. (6) Due to the smaller numbers of RCTs included in this NMA investigating soft stabilization splints and prefabricated splints, more RCTs are needed before a final decision can be made. (7) Most of the RCTs included in the arthrogenous TMD analyses were on disc displacement with reduction. However, disc displacement without reduction, closed lock, and TMJ arthralgia were included in some RCTs; thus, the reader should interpret the present results with great caution, taking this heterogeneity into consideration.

The advantages of this study are (1) that it includes 48 RCTs investigating the efficacy of different occlusal splints (hard stabilization splint, soft stabilization splint, anterior repositioning splint, non-occluding splint, and mini-anterior splints) and counselling therapy with or without a hard stabilization splint in patients with TMDs, with the inclusion of untreated controls, using NMA. (2) NMA and meta-regression analysis were achieved to assess the effect of the duration of follow-up, types of TMD diagnosis subsets, and wearing time of the hard stabilization splint. (3) The GRADE system was performed for all outcomes in this study to identify the type of confidence. (4) The inclusion of only RCTs assessing TMDs (masticatory muscles or articular) and exclusion of RCTs dealing with myofascial pain. (5) As the hard stabilization splint has been used extensively in the treatment of TMDs, it was used as a reference group/comparator during the statistical analysis. However, the presentation of the main results was reported in comparison to the untreated control group and hard stabilization splint. (6) The classification of counselling therapy to include behaviour changes, muscle exercise, joint mobilization, self-management, professional reassurance, and relaxation sessions was done according to the definitions of the behaviour change taxonomy (version 1)[11]. (7) The sensitivity analysis was done by performing NMA after excluding RCTs that recruited patients with mixed TMDs.

Conclusions

In conclusion, all occlusal splints, such as the anterior repositioning splint, hard stabilization splint, soft stabilization splint, mini-anterior splint, and prefabricated splint, are probably more effective treatments for arthrogenous and myogenous TMDs when compared to no treatment (untreated control patients) and non-occluding splints.

For patients with mainly arthrogenous TMDs, low quality evidence suggests the anterior repositioning splint and counselling therapy in combination with a hard stabilization splint to be the most effective treatments in respect to reductions in pain and TMJ sounds. Very low quality evidence suggests that hard stabilization splints probably do little or provide no difference in the outcome of subjective pain when compared to soft stabilization splints.

Moderate quality evidence suggests that counselling therapy has comparable efficacy in pain improvement and post-treatment pain intensity to a hard stabilization splint alone; however, the same level of evidence suggests that the combination of a hard stabilization splint with counselling therapy may provide additional advantages over a hard stabilization splint alone. Very low quality evidence suggests mini-anterior splints such as the NTI-tss and anterior midline stop devices probably provide little or no difference in the outcome of subjective pain when compared to a hard stabilization splint alone.

For patients with mainly myogenous TMDs, there is very low certainty evidence that mini-anterior splints may be the most effective treatment in decreasing the outcome of subjective pain. Very low quality evidence indicates that both hard stabilization splints and soft stabilization splints produce similar results in the outcome of subjective pain. The additional use of a hard stabilization splint with counselling therapy provides minimal advantage over the use of counselling therapy alone (moderate quality evidence); thus, starting with low-cost counselling therapy is highly recommended before using a combination of counselling therapy and a hard stabilization splint. Low quality evidence suggests that the hard stabilization splint alone is an effective treatment in reducing signs and symptoms of myogenous TMDs when compared to no treatment (untreated control subjects) or treatment with non-occluding splints.

Finally, the results derived from this NMA of 48 RCTs lead to the rejection of the hypothesis that various occlusal splints, either alone or in combination with counselling therapy, yield similar outcomes in the management of TMDs. On the other hand, this NMA verifies the hypothesis that the hard stabilization splint achieves superior results in patients with myogenous TMDs in comparison to those with arthrogenous TMDs. This study also confirms a substantial association between the effectiveness of hard stabilization splints and the wearing time per day and the overall duration of follow-up; hence, the hypothesis of no association is rejected.

Competing interests

There is no conflict of interest to declare.

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Ethical approval

Not required.

Patient consent

Not required.

Appendix A. Supplementary data

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