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TREATMENT POSSIBILITIES FOR TEMPOROMANDIBULAR DISORDERS

Ph.D. Thesis

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„If the plan does not work, change the strategy but never the goal”

Fred Devito

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1. LIST OF ABBREVIATIONS

TMD	Temporomandibular Disorder
TMJ	Temporomandibular Joint
CI	Confidence Interval
MMO	Maximum Mouth Opening
NRS	Numerical Rating Scale
RCT	Randomized Clinical Trial
PRISMA	Preferred Reporting Items for Systematic Reviews ad Meta-Analyses
OHIP-14	Oral Health Impact Profile-14
SD	Standard Deviation
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
WHO	World Health Organization
NSAID	Nonsteroidal anti-inflammatory drug
GI	Gastrointestinal
MD	Mean Difference
NMA	Network Meta-Analysis
PRGF	Platelet-Rich Growth Factor
PRP	Platelet Rich Plasma
CS	Corticosteroid
DDWOR	Disc Displacement without Reduction
DDWR	Disc Displacement with Reduction
SUCRA	Surface Under the Cumulative Ranking
CBCT	Cone-Beam Computed Tomography
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
PDGF	Platelet-derived Growth Factor
HA	Hyaluronic Acid
iPrf	Injectable Platelet Rich Fibrin
GH	Glucoseamine-hydrochloride

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SH	Sodium hyaluronate
SR	Systematic review
MA	Meta-analysis
TENS	Transcutan Electrical Nerve Stimulation
MT	Manual Therapy

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2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to enhance patient care, thereby improving the quality of life for individuals with temporomandibular disorders. Additionally, I aim to develop a treatment protocol for TMD (Temporomandibular Disorders) that is accessible to all patients, regardless of the location of dental offices.

My mission is: to put emphasis on prevention and therapy by a multidisciplinary team and to have proper funding to increase the level of evidence.

My specific goals include the investigation of conservative therapeutic possibilities for myogenic and arthrogenic temporomandibular disorders, as well as the therapeutic possibilities for sleep bruxism.

2.2. Scientometrics

Number of all publications:	12
Cumulative IF:	36,3
Av IF/publication:	3,3
Ranking (Sci Mago):	D1: 11
Number of publications related to the subject of the thesis:	2
Cumulative IF:	6.4
Av IF/publication:	3.2
Ranking (Sci Mago):	D1: 2
Number of citations on Google Scholar:	6
Number of citations on MTMT (independent):	12
H-index:	1

The detailed bibliography of the student can be found on page 63.

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2.3. Future plans

In the future, my plans are centered on both advancing my theoretical knowledge and to enhance my skills in medical care as well. By participation of medical care, its obstacles and concerns can be implemented in research, thus a more focused approach can be achieved in patient treatment. I believe that combining research with clinical practice can improve not only the individualized patient care but education as well. I strongly believe that in this way new generation dentists will have a more comprehensive look in the fields.

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3. SUMMARY OF THE PH.D.

TMD is a complex, multifactorial disease and the treatment possibilities are quite controversial, however, because of its high common occurrence the importance of diagnosis and adequate treatment is necessary.

To analyze the most common treatment possibilities for both myogenic and arthrogenic TMD two meta-analyses and systematic reviews were conducted on the topic. The above-mentioned analyses evaluated the effectiveness of the conservative and semi-conservative approaches to the disorder, involving new modalities for arthrogenic TMD.

Our results suggest that physiotherapy, manual therapy, and counseling can be utilized in managing myogenic TMD, either with or without splint therapy. However, due to the minimal differences between baseline and 1-month values, our results could not confirm the effectiveness of combination therapy.

In the treatment of arthrogenic TMD, saline-PRP injections resulted in a clinically noticeable improvement in MMO (Maximum Mouth Opening) and pain perception in the short term. In the long term, both Saline-HA (saline-hyaluronic acid) and Saline-steroid injections effectively increased MMO, while Saline-PRP (saline- platelet rich plasma) produced the most pronounced reduction in pain.

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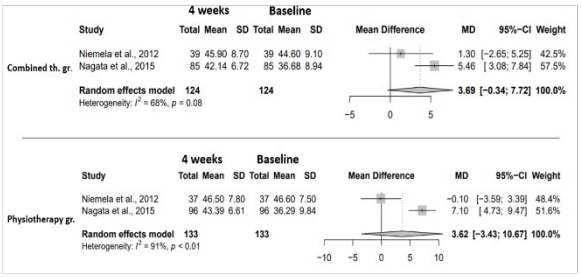
4. GRAPHICAL ABSTRACT

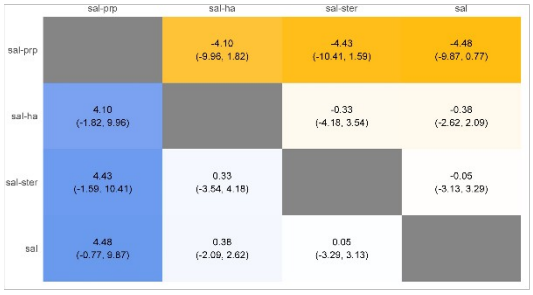
TREATMENT POSSIBILITIES FOR TEMPOROMANDIBULAR DISORDERS

OBJECTIVES: Evaluating the efficacy of different treatment modalities for myogenic and arthrogenic temporomandibular disorders, utilizing the most updated evidence-based literature.

Additional splint therapy has no superiority in myogenic temporomandibular disorders: A systematic review and meta-analysis of randomized controlled trials



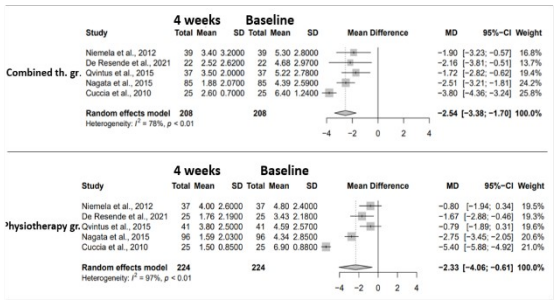
Forest plot of changes in maximum mouth opening between baseline and follow-up intervention group and control group



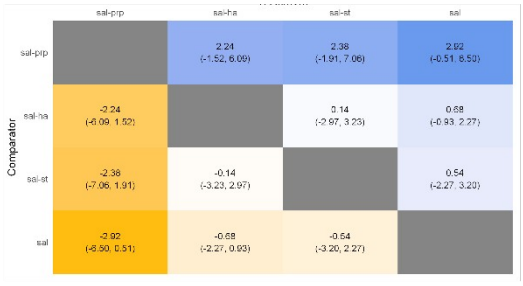
Direct and indirect comparison of treatment modalities in mm for maximum mouth opening at 1 month follow-up

Conclusion:
Additional splint therapy to physiotherapy, counseling and manual therapy has no superiority in myogenic temporomandibular disorders.

Efficacy of different intraarticular injection materials in the arthrocentesis of arthrogenic temporomandibular disorders: A systematic review and meta-analysis of randomized controlled trials



Forest plot of changes in pain perception between baseline and follow-up intervention and control group



Direct and indirect comparison of treatment modalities in mm for maximum mouth opening at 1 month follow-up

Conclusion:
Combination therapy with saline solution are effective, especially saline-PRP in both long and short term regarding maximum mouth opening and pain perception in arthrogenic TMD:

IMPLICATIONS: Improving patient care with a prompt diagnosis, implementing novel treatment possibilities with longer follow-ups.

CENTRE FOR TRANSLATIONAL MEDICINE

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5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Our primary focus is on evaluating conservative and semi-conservative treatment options for temporomandibular disorders, including both myogenic and arthrogenic cases.

5.1.2. What is the problem to solve?

There is no universal agreement on the best treatment strategy for temporomandibular disorders and the scientific evidence supporting the therapeutic possibilities is often limited and controversial.

5.1.3. What is the importance of the topic?

TMD is the third most common stomatological disorder which affects the masticatory system including the muscles and joints. [1] The main symptom of the disorder is pain, which has a prominent impact on patients' quality of life. [2]Besides this symptom, the limited functions are also crucial inferences that can lead to several challenges for patients. The unknown background and the lack of prompt etiology make healthcare workers face many obstacles in treatment possibilities.

5.1.4. What would be the impact of our research results?

Through a consistent assessment of different treatment possibilities for TMDs, including myogenic and arthrogenic disorders, the effectiveness of these modalities can be evaluated which have a prominent effect on patients' lifestyles, incorporating functional and psychological improvements. Using objective disease monitoring and diagnostic systems allow healthcare workers to personalize the treatment possibilities for patients.

5.2. Etiology of the disorder

TMD is a multifactorial and complex disorder that includes the masticatory system and has effects on the patient's functional movements and may affect the quality of life as well. The prevalence may range up to 15% in the adult population. [3]

Another study revealed that more than 41% of the population reported at least one symptom related to TMD and more than 50% showed a clinical sign of the disorder. [4], while the majority of patients are in their 20s-40s. [5] Some factors may contribute to the complexity of the disorder, like: trauma, both macro and microtrauma-like clenching, emotional stress in addition to deep pain input, and parafunctuonal activities. [6] All of the above-mentioned contributing factors must be taken into consideration in the management of TMD, while the treatment is often controversial due to the complexity of the disorder, the unknown prompt etiology, the lack of consensus on the treatment approaches and the patients' compliance with them. [7]

5.3. Diagnosis a key player in temporomandibual disorders

The recommended evidence-based new DC/TMD (Diagnostic Criteria for Temporomandibular Disorders) protocol is appropriate for use in both clinical and research settings. [8, 9]More comprehensive questions assess in further detail jaw functional limitations and psychological distress as well as additional constructs of anxiety and the presence of comorbid pain conditions. [8]

Moreover, imaging is a crucial diagnostic tool, however, the most frequently used panoramic radiography only reveals considerable changes in the osseous and cartilageous structures, thus its reliability is questionable. For TMJ (Temporomandibular Joint) pathology, MRI (Magnetic Resonance Imaging) or CBCT (Cone-Beam Computed Tomography) are the choice of diagnostic imaging depending on availability and the therapeutic indication. Despite the advancement in MRI imaging quality, it has not entirely overcome the limitations of the low-quality presentation of the complex osseous structure of the TMJ. CBCT is superior at identifying cortical bone contouring, remodeling, developmental abnormality, and pathological changes. Both imaging techniques have their limitations and remain complementary to each other in the TMJ diagnostic field. [10] However, the observers' experience might have a significant impact on the quality of these imaging systems. [11]

5.4. Conservative vs. non-conservative treatment possibilities

The therapeutic landscape of TMD is very controversial due to its origin, however the first-line treatment should always involve conservative treatment possibilities. These

treatment modalities aim to restore function and relieve pain with the demand of minimizing the need for more invasive interactions.

However, in some cases where these modalities may fail, more radical treatment or a combination of conservative therapies must be taken into consideration to optimize the symptoms of the patients. [12]

5.4.1. Conservative treatment possibilities

Conservative or reversible treatment possibilities are the first-line approaches in the management of TMD, as they are non-invasive, they have a localized effect on the TMJ. Moreover, they reduce side effects and are often well-tolerated and painless. The following treatment possibilities are considered as non-invasive modalities:

Physical therapy modalities include thermotherapy, cooling therapy, ultrasound, iontophoresis and transcutaneous electrical nerve stimulation, and laser therapy. [13]Thermotherapy increases the circulation of the applied area and also induces vasodilatation which reduces the myalgia. [14] On the other hand cooler therapy helps in the relaxation of the spasmed muscles and minimizes swelling. [15] These therapeutic possibilities provide immediate but short-term relief for the TMD symptoms. Both therapies act on the surface level, however, if a deeper input is necessary then ultrasound therapy can be used, as it increases the blood flow, and separates collagen, which results in the flexibility of the connective tissues. [16] With iontophoresis medications can be delivered directly through the skin to the painful area by using a low electrical current. [17, 18]Another approach that uses electrical stimulation is TENS, Transcutaneous Electrical Nerve Stimulation, which aims nerve endings to block pain signals to the brain, also stimulates blood flow and relax stiff muscles. [19] Manual therapy is a hands-on approach which aims to increase the range of motion, release tensions in muscles and address underlying muscle and joint discomforts. Soft tissue mobilization is an effective approach for managing muscle pain and involves both superficial and deep massage techniques. [20] Gentle massage over the affected area can help alleviate pain perception. Additionally, these techniques engage the patient actively in their treatment. Deep massage, while often more effective in restoring normal muscle function, requires a physical therapist. [21] Gentle

distraction of the joint can assist in reducing temporary adhesions and perhaps even mobilize the disc.

Pharmacologic therapy is a conservative approach, however, patients must be aware of their side effects.[22]

The most common side effects are gastrointestinal problems, including gastric reflux and stomach ulcers, in these cases proton pump inhibitor is suggested to be taken. [23] In some cases pharmacotherapy can be used with other conservative treatment possibilities, like physical therapy, that may offer the patient greater relief. [24]The most commonly used pharmacological agents are analgesics, antiinflammatories, muscle relaxants, anxiolytics, antidepressants, anticonvulsives, and muscular and intracapsular injections. [25]

Occlusal splint therapy is another conservative approach, that can be used in the treatment of the masticatory system. [26] Myalgia or arthralgia of the temporomandibualr joint can be treated. [27] Furthermore, patients with a history of bruxism can also apply for a splitnt therapy. [28]Different splint types aim to treat different conditions, moreover different diagnosis require different splint types. [29] The main occlusal splint types include permissive, semipermissive, and pseudopermissive splint. In treatment of TMD, the most frequently used splint type is the Michigan splint, a permissive splint. It achieves muscular function and avoids abnormal toothwear and connections, thus the muscular activity can be monitored. [30, 31]

Splint therapy is not only good in orofacial treatment, it is also beneficial on postural balance which is highly connected to TMD. [32] The usage of splint therapy is debatable in the literature, however it is still one of the most commonly used first-line treatment approach.[33] For short term Foude et al proved that splint therapy is more efficient than the control treatment, however for long-term, this superiority diminished. [34]

5.4.2. Semi-conservative treatment possibilities

90% of patients experience fewer symptoms with the first-line treatment, however, there are some severe cases, where a more invasive treatment is needed. [35] Arthrocentesis

can be utilized in these cases to reduce the symptomology of TMD. Ringer's solution, HA, and CS (corticosteroid) are the oldest materials that are used. However, newer treatment modalities such as platelet concentrations, and glucosamine show promising results. [36]

Normally the superior joint space is targeted, as it is the largest joint space and can be easily located. [37] During the procedures, medications are used to minimize the symptoms. [38]

Hyaluronic Acid is a naturally occurring glycosaminoglycan in the cartilage and in the synovial fluid. [39] It acts as a lubricant and mimics natural synovial fluid, reducing friction and pain. It also contributes to the production of endogenous HA. [40, 41]It also has an analgesic effect as it decreases the sensitivity of stretch-activated channels. Dosage: 1–2 mL injected into the joint space. The main indication of its usage is: For patients with osteoarthritis or chronic inflammation. [42] Corticosteroids are naturally occurring hormones, synthesized by the adrenal cortex. [43] Corticosteroids suppress inflammation and reduce pain after lavage by the inhibition of phospholipase A2, which reduces the synthesis of prostaglandins and leukotrienes. [44] CS can be used in 2 formulations for TMD injection based on their water solubility. [45] The insoluble way presents a slower release, thus they have longer effect, like: methylprednisolone acetate, betamethasone acetate, hydrocortisone acetate and triamcinolone acetonide (10-40mg). On the other hand, the soluble form works instantly, like dexamethasone sodium phosphate (4-8 mg) and betamethasone sodium phosphate. [46] PRP is an autologous medical device that is derived from liquid blood, it consists of platelets and growth factors. There are two other types of platelet concentrates, platelet-rich fibrin (PRF) and plasma rich in growth factors (PRGF). [47, 48] There are many protocols that must be followed to create PRP. The influencing factors can be: the isolation methods, the speed of centrifugation, and the processing time. [49, 50]

PRP promotes healing by delivering growth factors and also presents stimulates chondrocytes to engineer the cartilage and has a major impact on he biosynthesis of collagen and proteoglycans.[51, 52] The indication for PRP usage is for patients with degenerative joint changes or persistent pain. [53]

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During the procedure, acute malocclusion may happen on the ipsilateral side, as there is a volume growth in the joint space it causes a separation of the same side of the injection. Mild discomfort, swelling, and pain may occur during the procedure. [54]

Infection and bone necrosis may occur due to the mechanical irritation of the needle on the posterior part of the articular tuberculum. [55]

However, the incidence of these side effects is very low, and these complications mainly occur during arthroscopic surgery. [56]

The aftercare of the patients is also crucial, ice packs may reduce the swelling of the area, while NSAIDs (Nonsteroidal anti-inflammatory drug) have a great role in pain reduction, some muscle relaxants may reduce the tension in the area. [57]

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6. OBJECTIVES

6.1. Study I. – Additional splint therapy has no superiority in myogenic temporomandibular disorders

Even though previous systematic reviews and meta-analyses compared reversible treatment possibilities, the limitations were the high heterogeneity and the lack of high-quality evidence, making it difficult to observe consistent outcomes. Additionally, no meta-analysis has yet explored the most common combination therapies for myogenic TMD. Our review aims to narrow the intervention group to achieve more homogeneous results, comparing combination therapy (splint therapy along with physiotherapy, manual therapy, and counseling) and physiotherapy, manual therapy, and counseling in adults with myogenic TMD.

6.2. Study II. Efficacy of different intraarticular injection materials in the arthrocentesis of arthrogenic temporomandibular disorders

Despite a prior network meta-analysis conducted in this topic, which evaluated not only the conservative, minimally invasive but also the surgical treatment possibilities for arthrogenic TMD. The stage of the disorder was not mentioned, thus a high heterogeneity was observed in the diagnostic method and in the results.

This systematic review and network meta-analysis aimed to summarize the treatment outcomes of recent intraarticular devices developed for the management of arthrogenic TMD in a homogenous population, focusing on different follow-up periods.

7. METHODS

Both of the conducted MAs adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 recommendations. The Cochrane Handbook (https://training.cochrane.org/handbook) was used to conduct the reviews.

The studies were registered with Prospero (https://www.crd.york.ac.uk/prospero/) under the registration number Study I: CRD42021284777 Study II: CRD42022331212.

We systematically searched four databases: Cochrane Library (CENTRAL), Embase, MEDLINE (via PubMed), and Web of Science for all studies. The exact search date and the original queries are found in the original publications. In both studies case reports, meta-analyses, and reviews were omitted. Endnote X9.3.3 (Clarivate Analytics, Philadelphia, PA, USA) was utilized as the reference management tool during the selection process. Titles and abstracts of the records were screened then the automatic and manual removal of duplicate articles was evaluated. Full texts of the remaining articles were then reviewed to assess eligibility. Any disagreements between the two authors were resolved through consensus, involving a third author in the discussion when necessary.

The authors independently collected the following data from the included articles: year of publication, first author, type of study, demographic data, data on intervention and control groups, and the outcomes. Furthermore, for outcomes, we extracted baseline and post-intervention values in both the intervention and the control groups. When available, we included the change between the baseline and post-intervention results with the statistical analysis performed.

The revised Cochrane risk-of-bias tool for randomized trials (RoB2) was utilized to evaluate the risk of bias in both studies. [58] For Study I. the GRADE handbook, using the GRADE-PRO website. (https://www.gradepro.org/) was used for quality and certainty assessment. For Study II. the Confidence in Network Meta-Analysis tool was used to evaluate quality and certainty. [59]

The assessments were performed by two authors, in any case of disagreement a third author was involved.

7.1. Study I. – Additional splint therapy has no superiority in myogenic temporomandibular disorders

The eligibility criteria for Study I were based on our PICO (patient characteristics, type of intervention, control, and outcome) format. Two-armed interventional randomized controlled trials were included. The population was adult patients diagnosed with myogenic temporomandibular disorders; the intervention was combined therapy (splint + physiotherapy), the comparator was physiotherapy, manual therapy, and counseling, while the main outcomes were the extent of mouth opening and pain perception. Only English randomized controlled trials were monitored.

Patients with a history of head trauma, congenital abnormalities and mental, physical problems were excluded.

In Study I two kinds of meta-analysis were conducted, a „self-control" one, where the control and the treatment groups were compared to the baseline values, to conclude a statistically significant effect. In the second kind of meta-analysis the treatment and the control groups were compared to each other. A random effect model was used to pool the effect sizes. The standard deviation (SD) of the change from baseline was calculated by adding the baseline and follow-up time. Each follow-up time were evaulated separately. For Between-study heterogeneity the Cochrane Q test and Higgins and Thompson's I^2 statistics were used. Forest plots were used to graphically summarize the results. All statistical analyses were performed using R software (R Core Team 2020, ver. 4.1.3.) with the BugsNet package. [60]

7.2. Study II. – Efficacy of different intraarticular injection materials in the arthrocentesis of arthrogenic temporomandibular disorders

For Study II the PICO format was used, which included patient characteristics, type of intervention, control, and outcome. Based on our protocol, we included RCTs (Randomized Clinical Trials) investigating (P) adults (>18 years) with arthrogenic, Wilkes stage II-V TMD. As a network meta-analysis was conducted on all the medical devices that can be used for arthrocentesis. As outcomes: the extent of maximum mouth opening (MMO), protrusion, joint sound, and pain perception were measured.

Only studies that provided baseline and follow-up data were included. Moreover, only English articles were encompassed in the review.

In study II the mean differences (MD) and the standard deviations were evaulated according to the Cochrane Handbook. A network plot was created to check if the networks were fully connected. Pairwise Bayesian NMAs were performed. Random-effects models were used to calculate the pooled MD with a pre-specified 95% confidence interval (CI). A node-splitting analysis was performed to assess consistency. [61]

The surface under the cumulative ranking (SUCRA) curve values were calculated based on their posterior probabilities to rank different treatments. The pooled estimates from both direct and indirect comparisons with the results displayed in a forest plot. [62]

8. RESULTS

8.1. Study I. Additional splint therapy has no superiority in myogenic temporomandibular disorders

In the study selection 819 articles were identified, while 577 hits remained after the duplicate removal. 472 articles were excluded during the selections, Subsequently, 104 full-text records were retrieved, and 7 were included in the qualitative and quantitative syntheses. [63-69] **Figure 1** shows the selection process.

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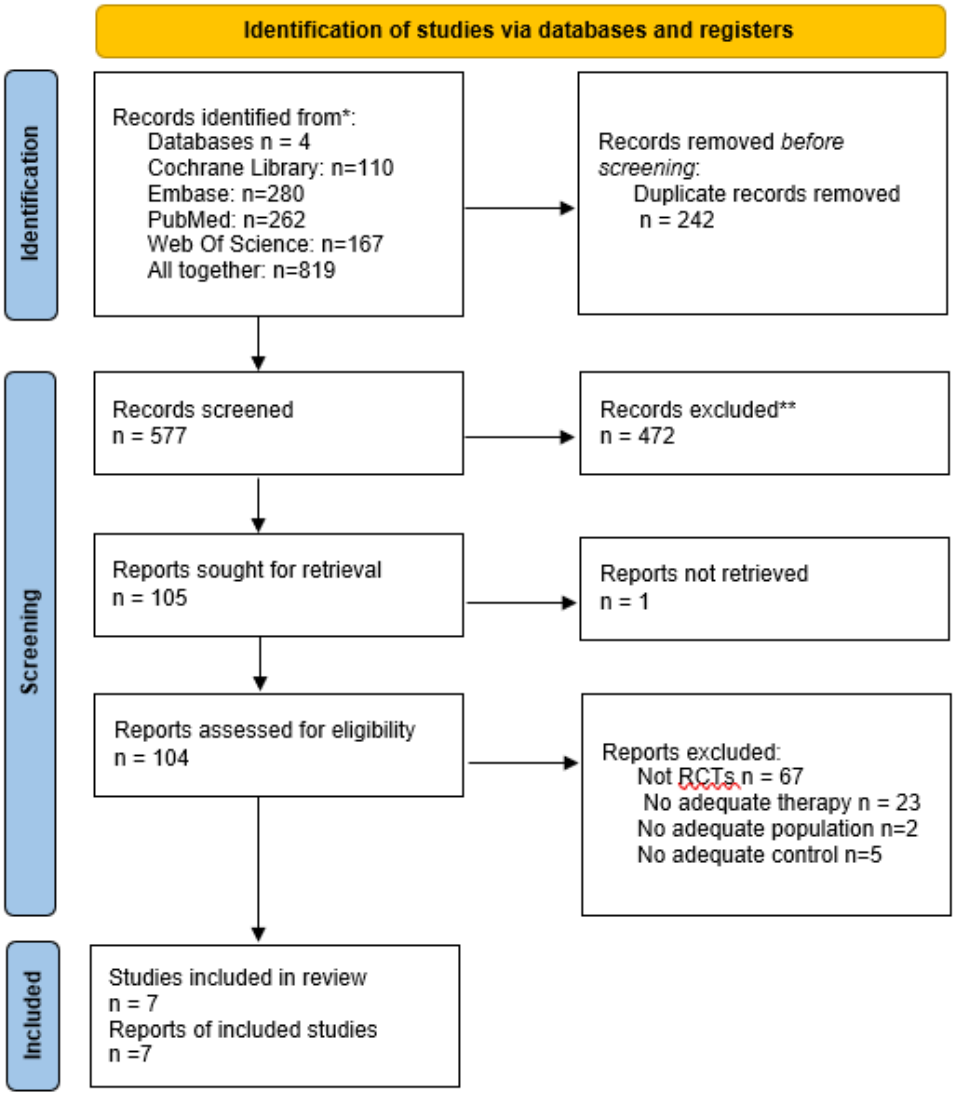

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA) flowchart for Study I. The basic characteristics of the included studies are shown in **Table 1.**

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Table 1. Basic characteristics of the included studies

First author, year of publication	Country	Study Type	Intervention	Control	Outcome	Diagnosis
Studies included in the meta-analysis						
Niemela 2012[63]	Finland	RCT	non splint multimodal therapy plus stabilization splint, counselling, masticatory muscle exercises	non splint multimodal therapy counselling, masticatory muscle exercises	Maximum mouth opening, pain perception	Myofascial pain
Kokkola 2018[68]	Finland	RCT	stabilization splint, counselling, masticatory	counselling, masticatory muscle exercises	Oral health related to quality of life	TMD related to oro and myofascial pain

First author, year of publication	Country	Study Type	Intervention	Control	Outcome	Diagnosis
			muscle exercises			
De Resende 2021[66]	Brazil	RCT	stabilization splint, counselling, masticatory muscle exercises	manual therapy	Oral health related quality of life, pain perception	orofacial pain
Katyayan 2013 [67]	India	RCT	stabilization splint, counselling, masticatory muscle exercises	counselling, masticatory muscle exercises	Maximum mouth opening, pain perception	Myofascial pain
Qvintus 2015 [69]	Finland	RCT	stabilization splint, self	counselling, muscle	Pain perception	myofascial pain

First author, year of publication	Country	Study Type	Intervention	Control	Outcome	Diagnosis
			exercise, cognitive therapy, education and jaw manipulation	therapy		
Nagata 2015 [64]	Japana	RCT	stabilization splint, self-exercise, cognitive therapy, education and jaw manipulation	self-exercise, cognitive therapy	Maximum mouth opening, pain perception	Muscular disfunction

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First author, year of publication	Country	Study Type	Intervention	Control	Outcome	Diagnosis
Cuccia 2010 [65]	Italy	RCT	splint therapy, physiotherapy, NSAIDs	physiotherapy, NSAIDs	Pain perception	-

Main characteristics of the included studies for Study I.

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a. Maximum mouth opening

The MMO was measured in mm using a caliper or ruler. An analysis was conducted on the baseline and 1-month follow-up changes between the intervention and the control group using 2 articles. The results are shown in Figure 2. In this analysis, a 0.07 mm difference was detected, which is statistically insignificant and clinically irrelevant. The effect size in the intervention group was 3.69 (95% CI: -0.34;7.72) in mm, while in the comparator group it was 3.62 (95% CI: -3.43;10.67) in mm. [63, 64]

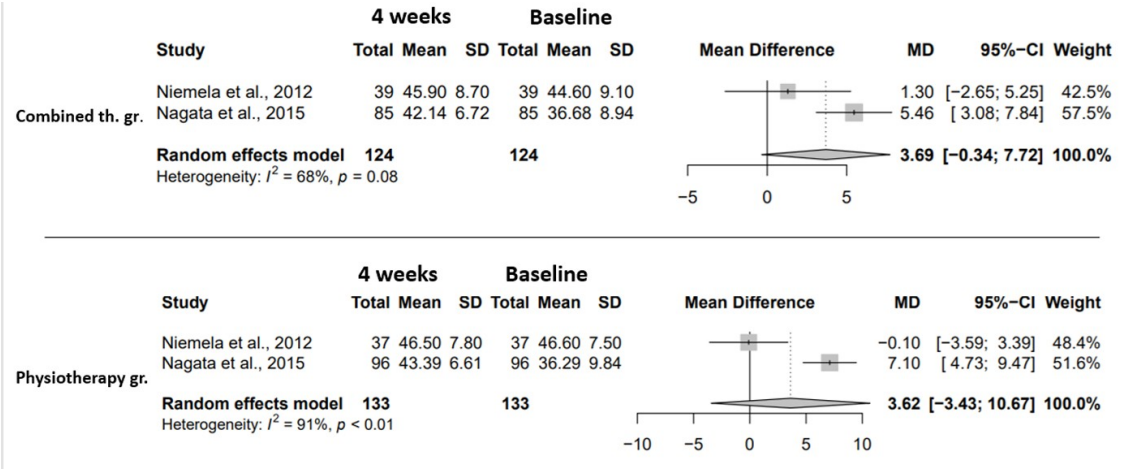

Figure 2: Forest plot of changes in MMO between baseline and 1-month follow-up in the intervention and control group. In the intervention group the effect size was 3.69 (95% CI: -0.34;7.72) in mm, while in the comparator group it was 3.62 (95% CI: -3.43;10.67) in mm.

Another analysis was performed at 1-month follow-up, comparing two articles. [63, 64] The effect size was -1.11 (95% CI: -2.83;0.61) with low heterogeneity(I2=0%). The results showed a modest decrease in the intervention group. The overall effect was statistically insignificant and clinically not relevant.(Figure 3)

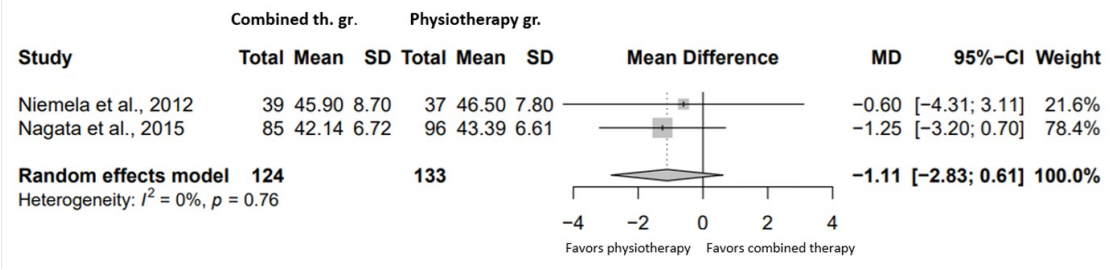

Figure 3: Forest plot of 1-month values for MMO, the effect size was -1.11 (95% CI: -2.83;0.61) with low heterogeneity(I2=0%).

An additional analysis was implemented to double-check the randomization of the groups. The baseline values were analyzed to determine differences in the included articles. 4 articles were included, with an effect of -0.62 (95% CI: -1.28;0.03) mm, which showed no significant difference between the intervention and the control group, so the randomization is considered to be sufficient. (Figure 4) [63-65, 67]

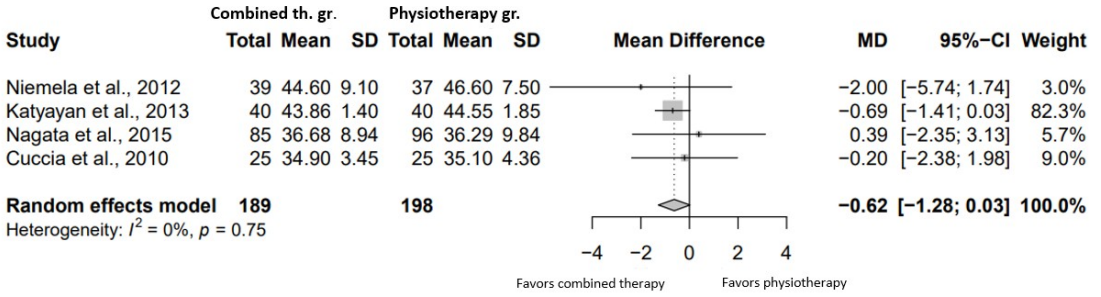

Figure 4: Forest plot of baseline values in MMO, the effect size was -0.62 (95% CI: -1.28;0.03) mm.

b. Pain perception

Pain perception was measured using the visual analog scale or the numerical rating scale (NRS). As the pain perception is highly influenced by many factors, it is considered as a secondary outcome.

The baseline and 1-month follow-up results of the intervention and control groups were analyzed in five articles. In the intervention group, the effect size was -2.54 (95% CI: -3.38; -1.70), while in the comparator group it was -2.33 (95% CI: -4.06; -0.61). There is a slight difference between the two groups which is clinically not relevant and statistically not significant. (Figure 5) [63-66, 69]

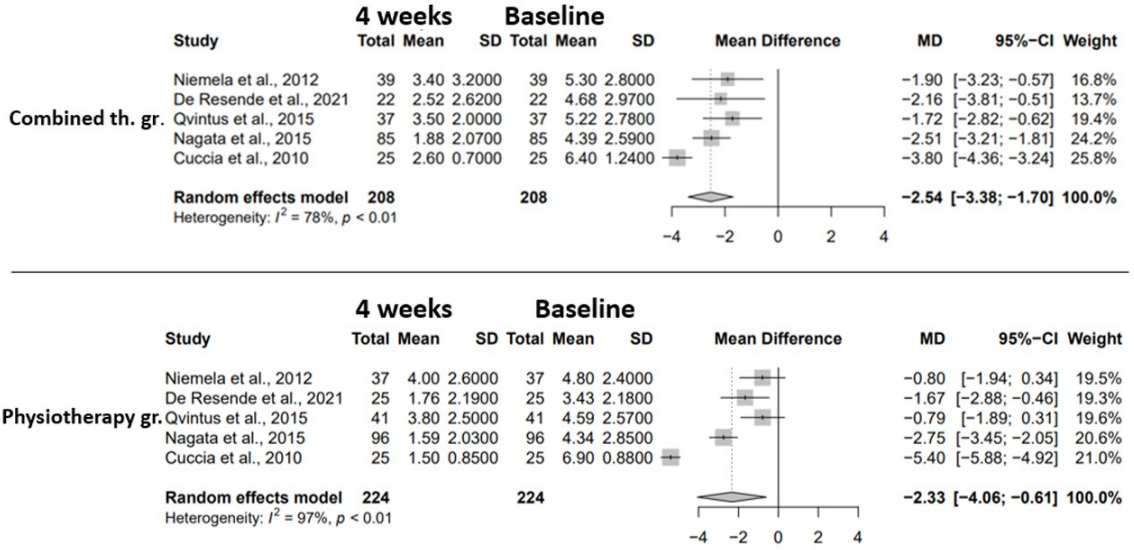

Figure 5: Forest plot of changes in pain perception between baseline and 1-month follow-up in the intervention and control group. In the intervention group, the effect size was -2.54 (95% CI: -3.38; -1.70), while in the comparator group it was -2.33 (95% CI: -4.06;-0.61).

6 articles were included in the baseline values analysis, where the effect size was 0.01 (95% CI: -0.61;0.63). As the confidence interval of Katyayan (95% CI: -1.11; -0.24) was beyond the overall CI (95% CI: -0.61;0.63), the result suggested that the randomization was not carried out perfectly, thus the article was excluded from the analysis. (Figure 6) [63-67, 69]

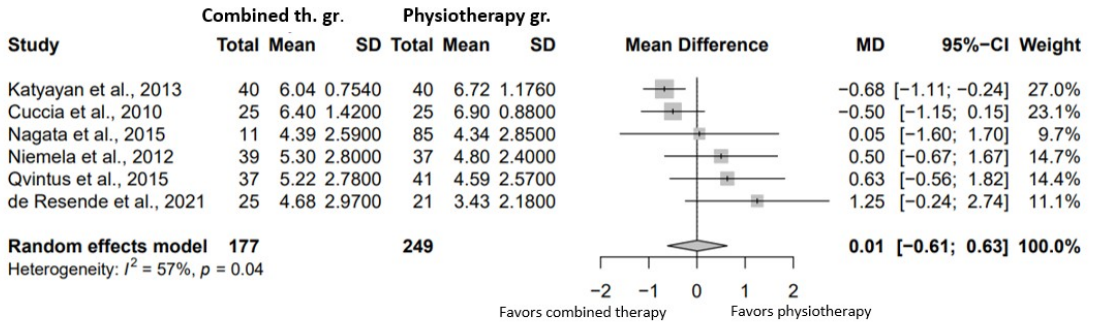

Figure 6: Forest plot of baseline values in pain perception with the effcet size of 0.01 (95% CI: -0.61;0.63)

The 1-month results were reported from four articles, Cuccia et al was also excluded as the participants could take some painkillers which had influenced the results. The effect size was -0.03 (95% CI: -0.64;0.58), which is neither clinically nor statistically relevant. (Figure 7) [63, 64, 66, 69]

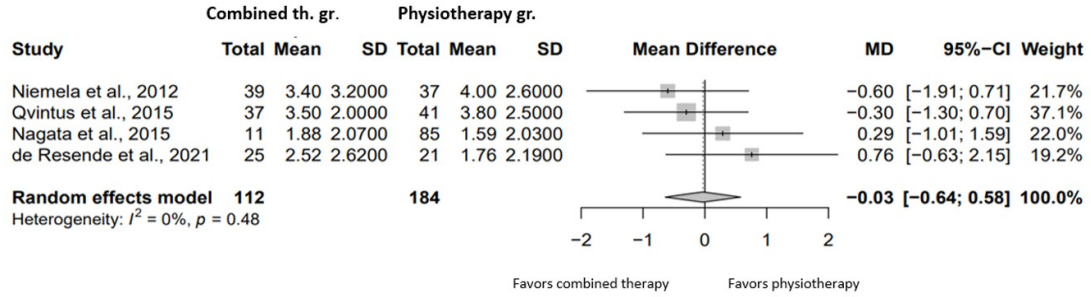

Figure 7: Forest plot of 1-month values for pain perception, the effect size was -0.03 (95% CI: -0.64;0.58).

8.2. Study II. Efficacy of different intraarticular injection materials in the arthrocentesis of arthrogenic temporomandibular disorders

After the searching process 7674 artciles were found, after the duplicate removal 5685 remained. 5464 hits were excluded,yielding 58 RCTs full-texts. 25 RCTs were included in the qualitative synthesis, while 13 were used in the quantitative analysis. The selection process is shown in Figure 8. [40, 70-82]

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PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

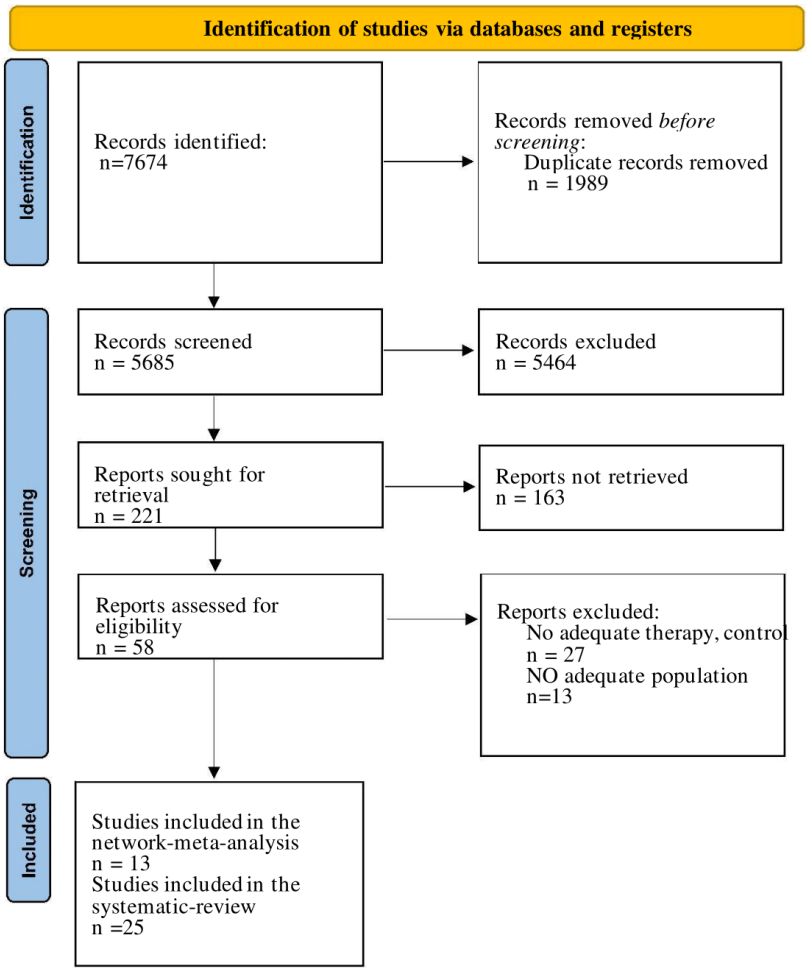

Figure 8: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA) flowchart for Study II.

The basic characteristic table of the included articles are found in **Table 2.**

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Table 2. Basic characteristics of the included studies

First author, year of publication	Study Type	Diagnosis	Intervention	Control	Follow-up period
Studies included in the meta-analysis					
Bouloux 2016[70]	RCT	Wilkes II, III, IV	Ringer + CS and Ringer+HA	Ringer	1,3 months
Bergstrand 2019[40]	RCT	Osteoarthritis	Ringer + 1 ml HA	Ringer	6 months
Gurung 2017[76]	RCT	Osteoarthritis	Ringer + a.5 ml HA	Ringer	1 week, 1,2,3 months
Hegab 2015[78]	RCT	Osteoarthritis	Ringer + 1ml HA	50 ml Ringer + 1 ml PRP	12 months
Karadayi 2021[79]	RCT	Wilkes III, IV, V	Ringer + iPrf	Ringer	1,3 months
Kilic 2016[71]	RCT	osteoarthritis	100 ml Ringer + 1 ml CS	100 ml Ringer	12 months
Ozdamar 2016[80]	RCT	Internal derangeme	Ringer + 2 ml SH	200 ml Ringer	1 week, 1,3 months

First author, year of publication	Study Type	Diagnosis	Intervention	Control	Follow-up period
		nt, Wilkes III			
Patel 2016[81]	RCT	Internal derangement	Ringer 1 ml SH	200 ml Ringer	1 week, 1,3,6 months
Tabrizi 2014[82]	RCT	Internal derangement	Ringer + 8 mg CS	200 ml Ringer	1,6 months
Dolwick 2020[74]	RCT	Muscle diagnosis group1, disc displacement group2, degenerative joint	Ringer + 20 mg CS	100 ml Ringer	2,3 months

First author, year of publication	Study Type	Diagnosis	Intervention	Control	Follow-up period
		table group3			
Hanci 2015[77]	RCT	Anterior disc dislocation with reduction	Ringer + 0.6 ml PRP	100 ml Ringer	1 week, 3,6 months
Kilic 2015[72]	RCT	Osteoarthitis	100 ml Ringer + 1 ml PRP	100 ml Ringer	12 months
Kilic 2021[73]	RCT	Osteoarthritis	Ringer + 20 mg HA	Ringer+ HA + GH+ CS	12 months

Main characteristics of the included studies for Study II.: PRP-platelet-rich plasma, iPrf: injectable Platelet Rich Fibrin, HA: hyaluronic acid, GH: glucosamine hydrochlorid, CS: corticosteroid, SH: sodium hyaluronate

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a. Maximum mouth opening

The MMO was analysed in 3 different follow-ups: 1,3,12 months after the intervention with the help of a ruler or a caliper in mm.

For the 1-month follow-up 6 studies were included in the network meta-analysis. [70, 76, 79-82] The different treatments were ranked by calculating the surface under the cumulative ranking (SUCRA) curve values based on their posterior probability, with the highest ranking of saline-PRP (94.8%), where the effect size was: 4.48 mm (95% CI: –0.77, 9.87). The result is clinically relevant, as it shows a 4.48 mm increase in MMO. (Figure 9,10)

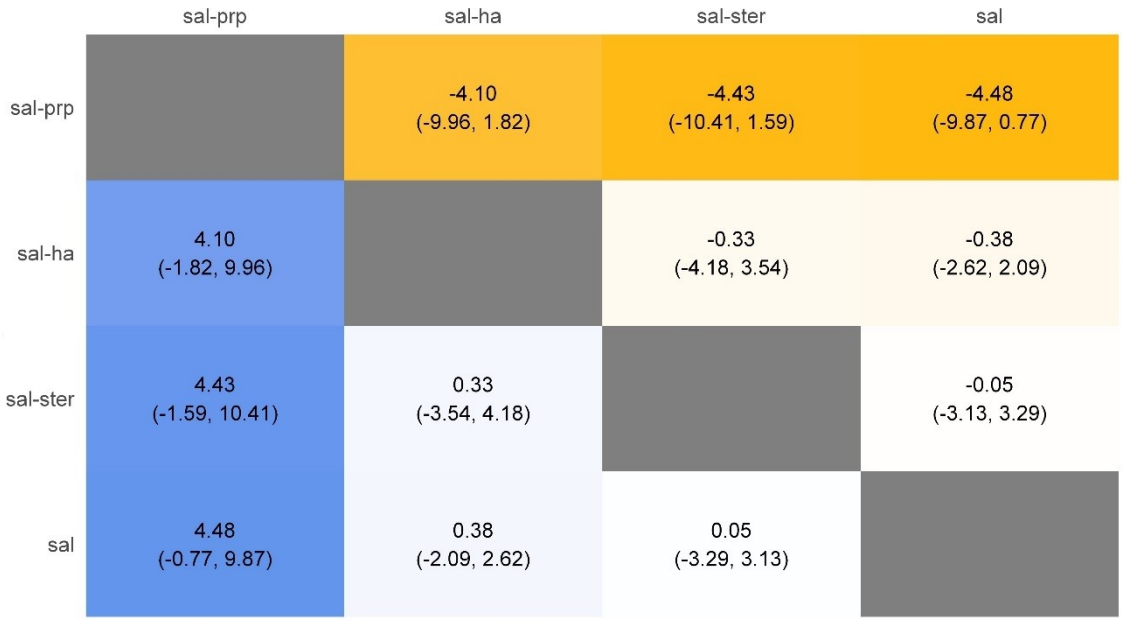

Figure 9: League heat plot of direct and indirect comparisons of the included treatments, with the best ranking of saline-PRP (94.8%), where the effect size was: 4.48 mm (95% CI: –0.77, 9.87).

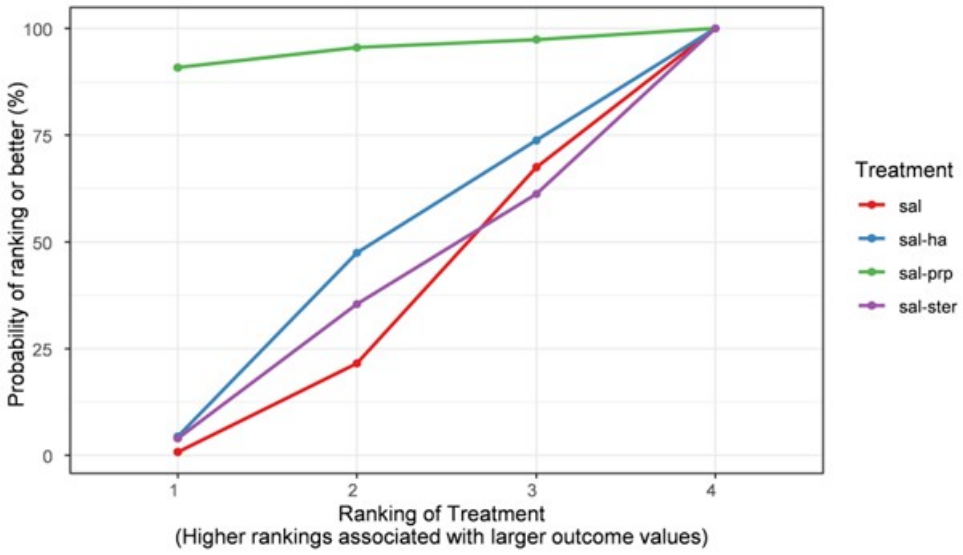

Figure 10: The SUCRA plot shows the highest ranking of saline-PRP with 94.8%.The surface under the cumulative ranking (SUCRA) curve values based on their posterior probability.

7 studies were included for the 3-month follow-up, where the effects of saline-steroid and saline-PRP were MD=3.36 mm (CI: –4.70, 10.46) and MD=3.49 mm (CI: –4.23, 10.81). The effects are clinically relevant, as they show a 3.36- and 3.49-mm increase in MMO. The treatments included were saline-PRP, saline-steroid, saline-hyaluronic acid and saline. (Figure 11,12) [70, 74, 76, 77, 79-81]

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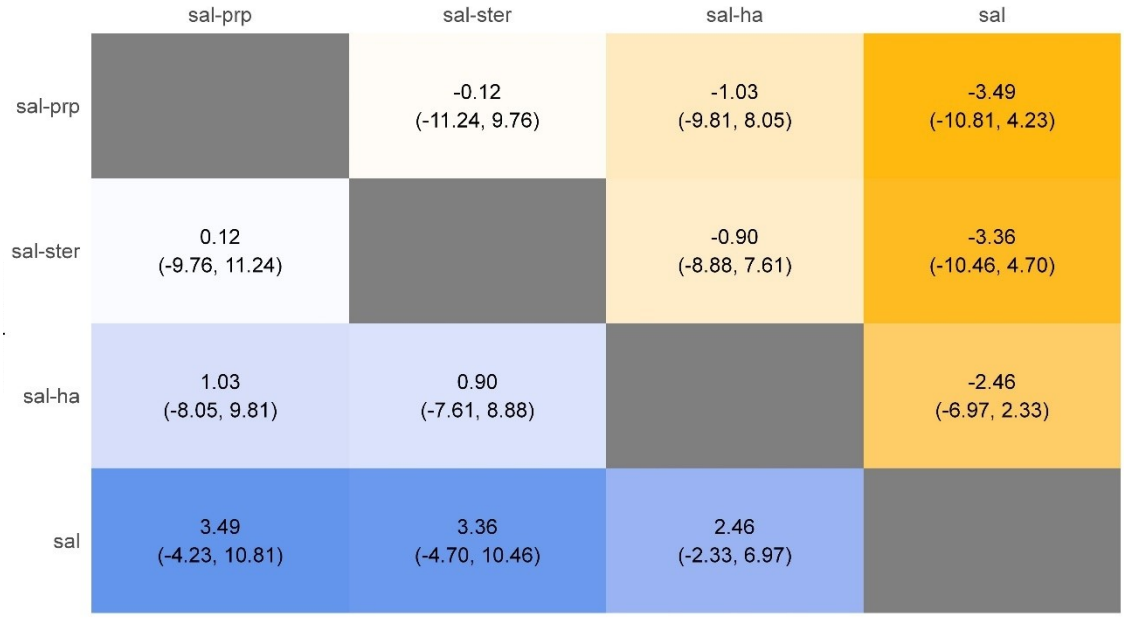

Figure 11: League heat plot of direct and indirect comparisons of the included treatments, with the best ranking of saline-PRP, where the effect size was: 3.49 mm (95% CI: –4.23, 10.81).

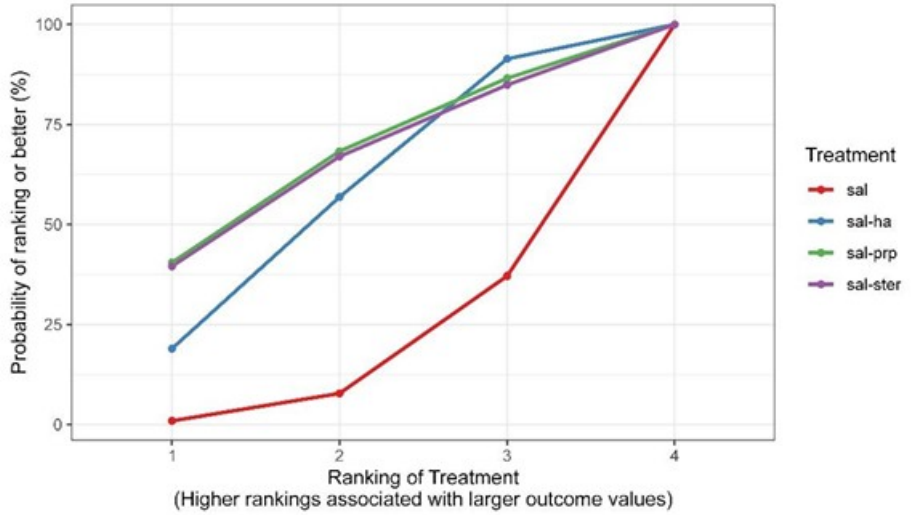

Figure 12: The surface under the cumulative ranking (SUCRA) curve values based on their posterior probability. The SUCRA values of the saline-PRP and saline-steroid were 37.8% respectively.

4 studies were included for the analysis of 12-month, the saline-HA with glucoseamin ranked as the highest with the effect size of 3.07 mm (95% CI: –2.06, 8.41). The saline-streoid had the same effect with 3.07 (CI: –4.34, 10.24) in MD. (Figure 13,14) [71-73, 78]

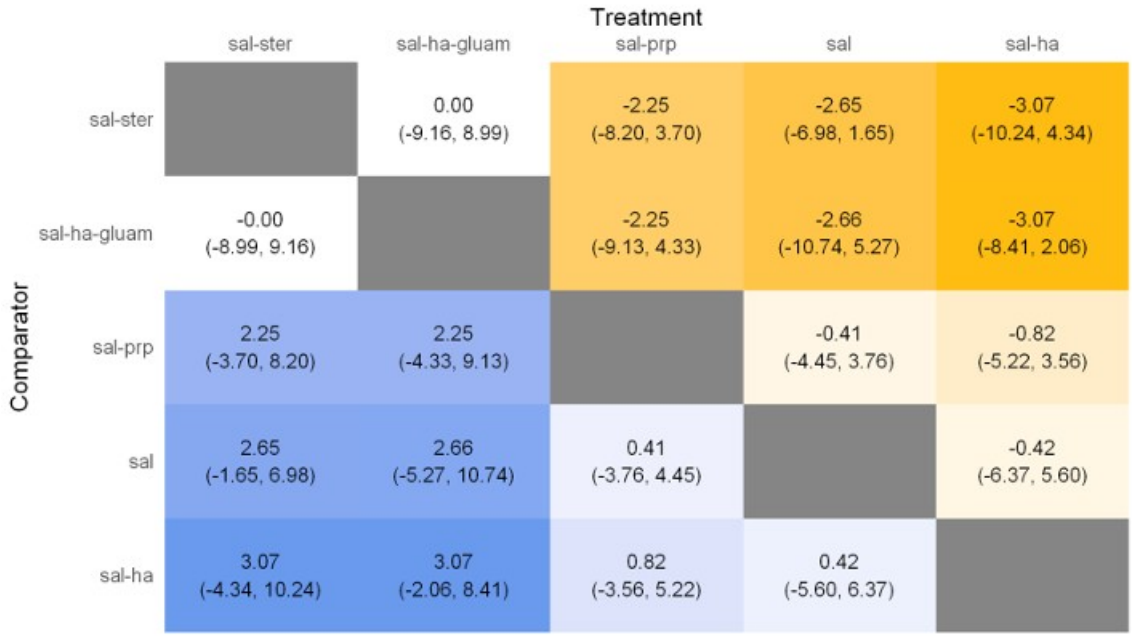

Figure 13: League heat plot of direct and indirect comparisons of the included treatments, with the best ranking of saline-steroid, where the effect size was: 3.07mm (95% CI: –4.34, 10.24).

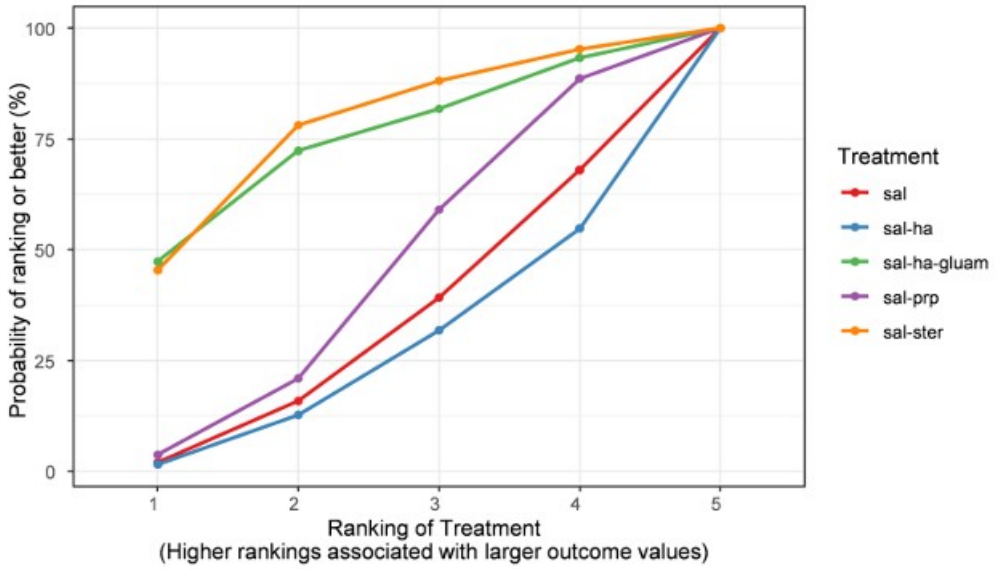

Figure 14: The surface under the cumulative ranking (SUCRA) curve values based on their posterior probability.

b. Pain perception

The pain perception was measured on a numeric rating scale, scoring from 0 to 10, as this outcome was highly subjective it is considered as a secondary outcome. The outcome was analysed in 3 follow-up periods.

For the 1-month follow-up 5 studies were included, saline-PRP reached a clincally relevant result with the effect size of -2.89 (95% CI: –6.17, 0.57) in MD. It means that the pain perception reduced with 2.89 in patients who got the saline-PRP treatment. The other treatments did not reach a clinically relevant level, as saline-HA resulted in -0.72 (95% CI: -2.35; 0.93). (Figure 15,16) [76, 79-82]

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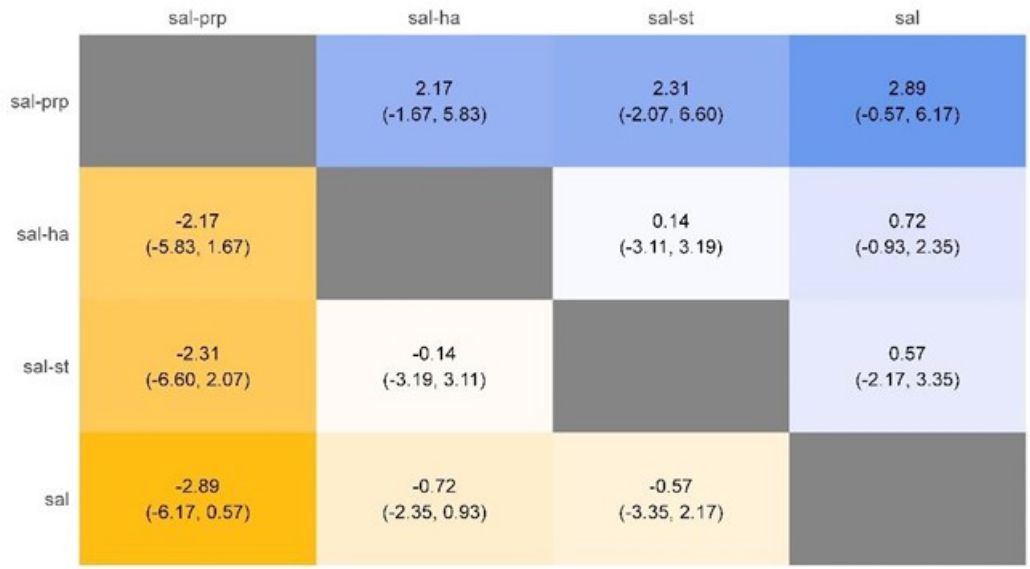

Figure 15: League heat plot of direct and indirect comparisons of the included treatments, with the best ranking of saline-PRP, where the effect size was: -2.89 (95% CI: –6.17;0.57).

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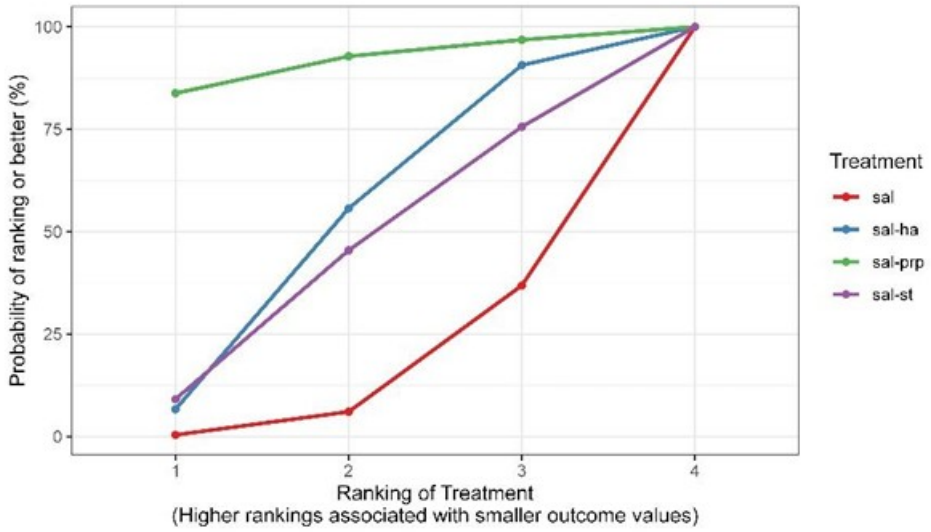

Figure 16: The surface under the cumulative ranking (SUCRA) curve values based on their posterior probability.

For the medium-term follow-up 3 months, still the saline-PRP reached the best ranking with the effect of MD=–2.72 (95% CI: –5.80, 0.35), with 78%. The second ranking was very similar to the 1-month follow-up result, as saline- HA reached a decrease with 1.01 (95% CI: -2.63;0.70) on the NRS. (Figure 17,18) [74, 76, 77, 79-81]

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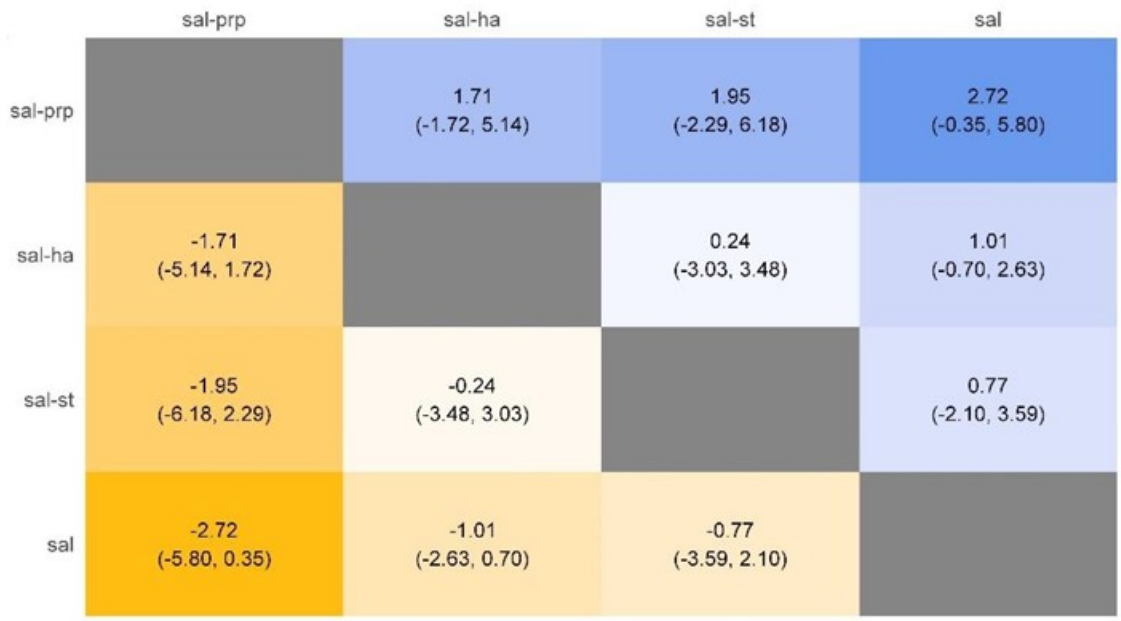

Figure 17: League heat plot of direct and indirect comparisons of the included treatments, with the best ranking of saline-PRP, where the effect size was: -2.72 (95% CI: –5.80, 0.35).

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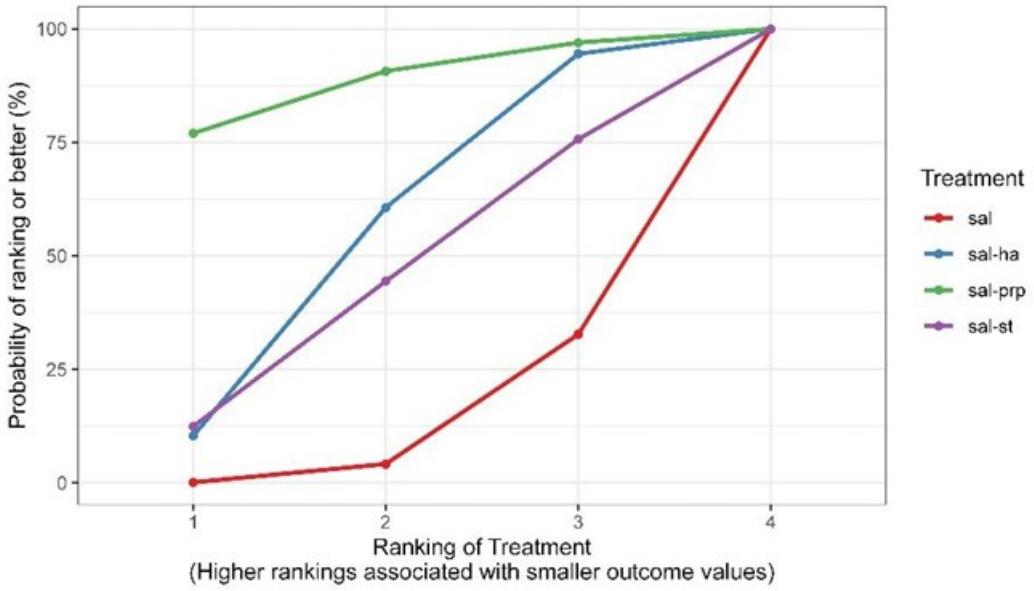

Figure 18: The surface under the cumulative ranking (SUCRA) curve values based on their posterior probability.

For the 1-year follow-up 4 studies were included, the saline-PRP resulted in (MD=–1.86, 95% CI: –5.72, 2.18), with the highest ranking of 73.5%. The saline usage decreased the pain perception with 1.44 (95% CI: –5.72, 2.18), while the saline-steroid resulted in a decrease with 1.14 (95% CI: -9.45; 7.24). (Figure 19,20) [71-73, 78]

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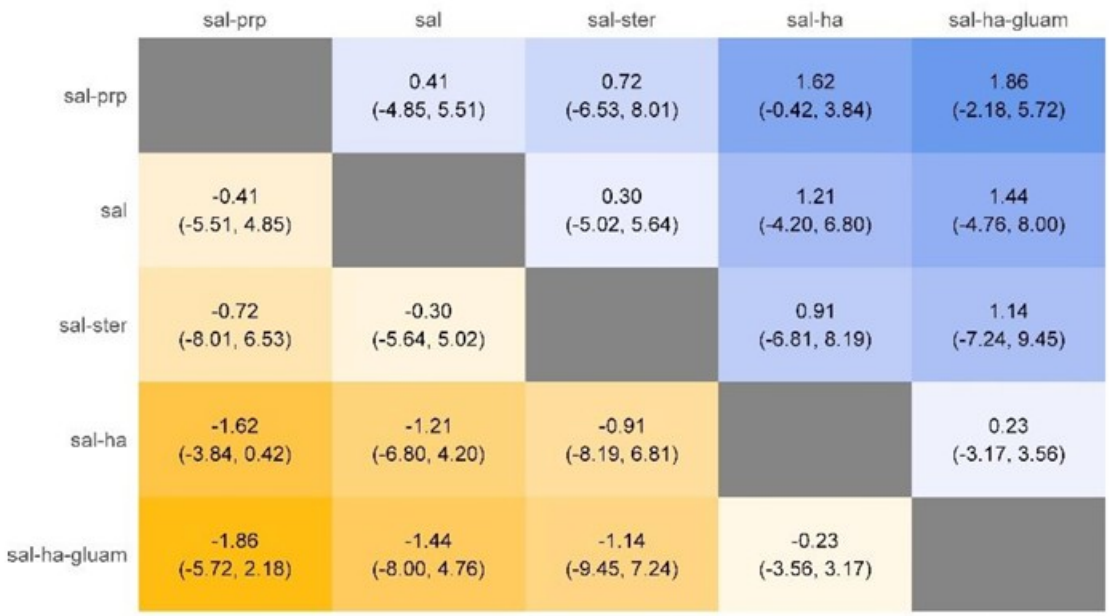

Figure 19: League heat plot of direct and indirect comparisons of the included treatments, with the best ranking of saline-PRP, where the effect size was: -0.41 (95% CI: –5.51, 4.85).

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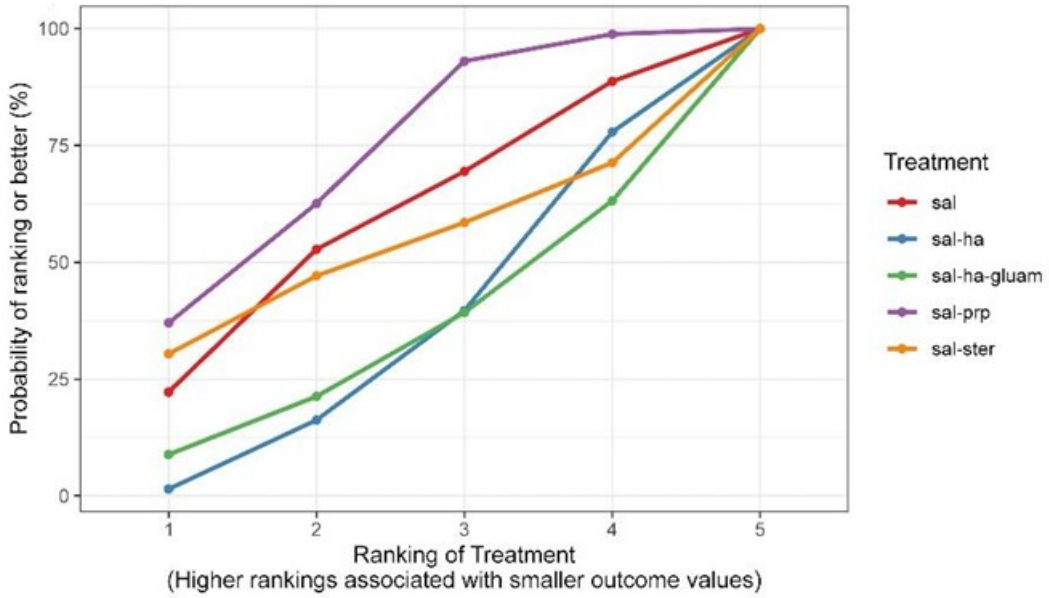

Figure 20: The surface under the cumulative ranking (SUCRA) curve values based on their posterior probability.

9. DISCUSSION

9.1. Summary of findings, international comparisons

Due to the complexity of temporomandibular disorders, there is an increasing focus on its therapeutic possibilities, especially on the first-line treatments due to their noninvasive nature. [83]As proper treatment and diagnosis is essential in-patient care; our objective goal was to assess the efficacy of different treatment modalities for TMD.

Due to the analysis we aimed to provide evidence-based solutions to clinical decision makers to treat the disorder appropiriately. Regarding the treatment of myogenic TMD we observed that both combination therapy- splint therapy along with physiotherapy, manual therapy, and counselling) and manual therapy, physiotherapy and counseling therapy alone can be used for the treatment of myogenic TMD. However, there was no clinically relevant difference between the treatment modalities,suggesting that the splint therapy usage might be questionable. Our findings correlate with another systematic review and meta-analysis by Armijo-Olivo et al. [21] According to their SR and MA physiotherapy especially passive and active stretching performed a great increase of maximum mouth opening and in pain reduction. However, the outcomes of the treatment depend on the patient's compliance, which may influence the result. Also, in some cases these exercise programs are not performed alone, but with many other therapeutic possibilities, thus a clear infromation is not provided about their efficacy. They also assessed the efficacy of manual therapy in the cervical spine and in the orofacial region. They concluded that it was more effective than home exercises, reducing pain perception and improving functions. Moreover, the MT of the cervical spine might have a great impact of treating TMD, as the 2 systems are connected in the trigeminocervical nucleus.[84]

Miller et al conducted a SR, evaulating the efficacy of MT and exercises alone and in combination to treat neck pain, whic was connected to orofacial pain. High quality evidence supported the efficacy of manual therapy with exercise therapy in short-term. [85]

Medlicott et al conducted a meta-analysis focusing on conservative treatment approaches, they concluded that active stretching of the muscles and manual

mobilization is effective in myogenic TMD. Furthermore, the combination therapies of active exercises, MT and biofeedback may be more effective than occlusal splint therapy. [86]

In some severe TMD cases where the fist-line treatment possibilities do not work, other more invasive procedures are needed in the treatment. In these cases, arthrocentesis can be performed. In our second SR and MA we aimed to assess the efficacy of the most used medical devices for arthrocentesis. We concluded that in short-term saline-PRP, saline-HA, and saline steroids demonstrated statistically insignificant results; however, saline-PRP injection increased MMO remarkably. Both saline-PRP and saline-steroid were effective in MMO in long-term, however the best clinical parameters were achieved by the saline-PRP combination. All the treatment modalities provided clinical improvements regarding the symptomology of the disorder. Liu et al conducted a MA and SR of intraarticular injections for osteoarthritis, including HA, dexamethasone, prednisolone, betamethasone, and betamethasone with HA, morphine, tramadol, platelet-derived growth factor (PDGF), placebo, and Ringer's solution. For maximum mouth opening tramadol and PDGF were the most efficient, however one of their limitations was the small number of studies involved in the analysis. [87] Al-Moraissi et al systematically searched for treatment approaches, including both minimal invasive and surgical modalities. However the stage of the disorder was not mentioned in details, thus a heterogeneity was observed. Even though the limitations, it was a comprehensive summary of the recently used treatments. They concluded that with intraarticular injections combined with HA, PRP or CS, clinically significant improvements can be reached than with conservative ones in both long and short-term as well. The most effective treatments are: arthroscopy procedures followed by arthrocentesis, especially in combination with PRP and HA. The conservative treatments have a lower quality of evidence regarding th esymptomology. [88]

Vingender et al found similar outcomes inbetween HA and PRP for arthrocentesis, however it was advised to use autologous medical devices to avoid and possible adverse effects.[89] In the treatment not only the used material is essential, but the diagnosis as well.

Nardini et al reported that arthrocentesis was the most effective in cases, where the diagnosis was disc displacement without reduction, closed lock, or osteoarthritis. [75] The efficacy of arthrocentesis in orthopedic literature has been provided for more than 30 years. [90] Ont he other hand, there are some cases where even more invasive approaches are needed, like: fibrous ankyloses, neoplasia, severe dislocation, and osteoarthrosis. [91]

9.2. Strengths

The main strength of the first meta-analysis and systematic review is that RCTs were involved in the analysis, using the Diagnostic Criteria for Temporomandibular Disorders. In the intervention group the Michigan splint was used under same circumstances. Moreover, other reverse conservative therapies were involved in the analysis. Regarding the second meta-anaylsis and systematic review the strengths of this study include its exclusive reliance on RCTs and standardized diagnostic criteria for TMD, ensuring a uniformly diagnosed population. Furthermore, all medical devices were thoroughly evaluated through both indirect and direct network analyses. The incorporation of diverse follow-up periods allowed for a comprehensive assessment of both short- and long-term efficacy.

9.3. Limitations

In our first study, only a short-term follow-up period was involved, thus the long-term efficacy of the different materials cannot be concluded. Furthermore, a small number of studies could be used, that might have affected the outcome. In Cuccia et al [65] additional pharmacotherapy was used, and because of its analgesic effect that could influence the effect of pain perception. While physiotherapy, manual therapy, and counseling are recognized treatment modalities, their implementation in daily clinical practice can be challenging. Additionally, their success heavily relies on patient compliance, which may limit their effectiveness in certain cases due to the varying nature of the disorder.

The limitation of the second study is that the exact PRP preparation method was not investigated in the included studies. The classification of arthrogenic TMDs was not used consistently, thus the population of the studies remained heterogenous. The dosage

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of the medical devices differed, which could have affected the outcomes. Moreover, other approaches, like non-invasive therapies were not involved in the study. Only the maximum mouth opening and pain perception was evaluated in the study.

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10. CONCLUSION

For the conservative treatment of temporomandibular disorders combination therapy and physiotherapy can be used, however, a slight difference was observed between the two groups, thus the usage of additional splint therapy can be questioned. Moreover, regarding the results a multidisciplinary team should be emphasized, especially drawing attention to physiotherapy more. Relating to the treatment of arthrogenic temporomandibular disorders, the intraarticular joint lavage showed promising outcomes, particularly the PRP-saline combination therapy yielded a remarkable increase both in mouth opening and pain reduction. Saline-steroid combination therapy showed a prominent enhancement for both outcomes; however, the side effects of the treatment must be considered.

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11. IMPLEMENTATION FOR PRACTICE

Clinicians must use a consistent diagnostic tool, such as RDC/TMD that would be an objective addition that could help clinicians' decision-making regarding therapies.

Both RDC/TMD axes must be investigated thoroughly as not only clinical diagnosis but also the psychosocial assessment is crucial. If the proper diagnosis is done, then the population can be easily classified, thus more homogenous group of people can be investigated. In the first case, minimal invasive aspects should also be utilized as these are safe, financially beneficial, and can be used even at the first visit. These approaches have a reverse impact and can be combined even with more minimal invasive or more invasive therapeutic methods. The additional splint usage must be reconsidered. Moreover, implementing physiotherapists in the treatment can be profitable. Regarding the semi-invasive therapies, PRP is a steroid-free treatment modality, it can be used without increasing the risk factors of steroid-related side effects.

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12. IMPLEMENTATION FOR RESEARCH

For a more comprehensive analysis, more RCTs should be conducted, focusing on a more homogenous population, including well-described interventions, and standardizing the follow-up periods for each outcome. These details must enhance the assessment of the treatment of temporomandibular disorders. A well-defined diagnostic criteria and imaging modalities must be applied for more homogenous results. Not only clinical assessment but the psychological and social factors must be evaluated to have a consistent patient population.

For a prompter diagnosis imaging techniques can be involved. For conservative therapies, the exact methodology must be described in a detailed manner for the patients' better follow-up.

More investigations should be done into different medical devices. Pharmacological agents have been used for many years in the treatment of TMD, however, the exact mechanism and the interference with different drugs must be examined. The dosage and the adverse events are also crucial. The gastrointestinal effect of the NSAIDs drugs is prevailing, and their combination with other drugs are also crucial. We suggest that a predefined dosage might be used for homogenous data, thus the efficacy of the used medical devices cannot be biased. Future studies should prioritize evaluating primary TMD outcomes, joint sounds, and protrusive movements in a standardized manner. The quality of patients' life must be monitored before and after treatement.Extending follow-up protocols beyond 6 months would facilitate the identification of additional differences between the treatment possibilities. This longer duration would support a more thorough evaluation offering deeper insights into the comparative effectiveness of each approach

Also, there is a need for a better reporting system, which includes descriptive statistics with median and IQR in addition to mean and standard deviation.

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13. IMPLEMENTATION FOR POLICYMAKERS

For policymakers it is essential to emphasize the proper treatment modalities for the disease and to integrate new approaches in the health care system. By engaging in the development of new therapies making patients enable to have the access of varying therapeutic approaches. It is also crucial to revise the current guidelines based on a high evidence level.

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14. FUTURE PERSPECTIVES

Looking at the future, the intraarticular injections and the new treatment modalities bring promising opportunities in the health care system, especially PRP shows beneficial potential for the treatment. Moreover, the gnatology field should be wider, engaging specialist from other departments, creating a multidisclinary team for a better understanding of the etiology and treatment parameters of the disorder.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Kelemen, Kata ; König, János ; Czumbel, Márk ; Szabó, Bence ; Hegyi, Péter ; Gerber, Gábor ; Borbély, Judit ;Mikulás, Krisztina ; Schmidt, Péter ; Hermann, Péter **(2023)**

Additional splint therapy has no superiority in myogenic temporomandibular disorders: A systematic review and meta-analysis of randomized controlled trials. **Journal Of Prosthodontic Research** 68 : 1 pp. 12-19. , 8 p.

D1, IF: 3.2

Kelemen, Kata ; König, János ; Szilárd Váncsa ; Szabó, Bence ; Hegyi, Péter ; Schmidt, Péter ; Hermann, Péter **(2024)**

Efficacy of different intraarticular injection materials in the arthrocentesis of arthrogenic temporomandibular disorders: A systematic review and network meta-analyis. **Journal Of Prosthodontic Research**

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16.2. Publications not related to the thesis

Komora, Péter ; Vámos, Orsolya ; Gede, Noémi ; Hegyi, Péter ; **Kelemen, Kata** ; Galvács, Adél ; Varga, Gábor ;Kerémi, Beáta ; Vág, János (2024) Comparison of bioactive material failure rates in vital pulp treatment of permanent matured teeth - a systematic review and network meta-analysis.**Scientific Reports** 14 : 1 Paper: 18421 , 23 p.

D1, IF: 3.8

König, János; **Kelemen, Kata** ; Váncsa, Szilárd ; Szabó, Bence ; Varga, Gábor ; Mikulás, Krisztina ; Borbély, Judit ;Hegyi, Péter ; Hermann, Péter (2024)

Comparative analysis of surgical and prosthetic rehabilitation in maxillectomy: A systematic review and meta-analysis on quality-of-life scores and objective speech and masticatory measurements. **Journal Of Prosthetic Dentistry**

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