REVIEWS

Platelet Concentrate Treatments for Temporomandibular Disorders: A Systematic Review and Meta-analysis

F.S. Al-Hamed[1], A. Hijazi[2], Q. Gao[1], Z. Badran[1,3], and F. Tamimi[1,4]

Abstract: ***Objectives:*** *This systematic review compared platelet concentrates (PCs) versus hyaluronic acid (HA) or saline/Ringer's solution injections as treatments of temporomandibular osteoarthritis and disc displacement in terms of pain and maximum mouth opening (MMO).*

Methods: *PubMed, Cochrane, and Scopus were searched up to March 6, 2020. Inclusion criteria were randomized clinical trials (RCTs). Exclusion criteria were case series, observational studies, animal studies, and reviews. The Effective Public Health Practice Project (EPHPP) quality assessment tool was used to assess the risk of bias in the included studies. The weighted mean difference was used to compare the results.*

Results: *Nine RCTs were included with a total of 407 patients. The numbers of joints treated were 262, 112, and 112 in the PC, HA, and saline groups, respectively. The quality of studies was rated as strong in 4 studies, moderate in 4 studies, and weak in 1 study. The meta-analysis revealed that PCs decreased pain visual analogue scale (VAS) scores compared to HA by an average of –1.11 (CI, –1.62 to –0.60;* P < *0.0001) and –0.57 (CI, –1.55 to 0.41;* P = *0.26) at 3 and 12 mo follow-up respectively. Also, the average decrease in pain scores with PC compared to saline was –1.33 (CI, –2.61 to –0.06;* P = *0.04), –2.07 (CI, –3.46 to –0.69;* P = *0.003), and –2.71 (CI, –4.69 to –0.72;* P = *0.008) at 3, 6, and 12 mo, respectively. Regarding MMO measurements, PC was comparable to HA, but it was significantly better than saline after 3 and 6 mo [2.9 mm (CI,1.47 to 4.3;* P < *0.0001), and 1.69 mm (CI, 0.13 to 3.25;* P = *0.03) respectively].*

Conclusion: *PC reduces pain VAS scores compared to HA during the first 3 m after treatment, and when compared to saline, it reduces pain and increases MMO for longer durations. However, due to differences between groups regarding PC preparation protocols and study heterogeneity, further standardized RCTs are required.*

Knowledge Transfer Statement: *This study provides researchers and clinicians with quantitative and qualitative analyses of the current evidence regarding the clinical outcomes of platelet concentrate injections in the treatment of temporomandibular joint osteoarthritis and disc displacement in terms of pain control and maximum mouth opening.*

Keywords: joints, mastication, osteoarthritis, pain, platelet-rich plasma, temporomandibular joint

Introduction

Temporomandibular disorders (TMDs) are diseases of multifactorial origin that affect temporomandibular joint (TMJ) articular surfaces as well as the surrounding masticatory muscles (Ahmad and Schiffman 2016). Myofascial pain dysfunction syndrome, disc displacement, joint osteoarthritis, hypermobility, dislocation, and ankylosis are among the most common TMDs. Disc displacement is an abnormal position of the articular disc in relation

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A supplemental appendix to this article is available online.

to the mandibular condyle. It classifies as disc displacement with or without reduction (Emshoff et al. 2002). TMJ-osteoarthritis (OA) is a degenerative change of the articulating surfaces of the joint (Stegenga 2001). The risk factors for TMDs include psychological stresses, malocclusion, and traumas. In addition, the multi-etiological background of TMDs may affect the decision of a proper treatment for those patients (Al-Moraissi et al. 2017). The most common clinical signs and symptoms of TMDs are joint sounds, pain, restricted jaw movement, and joint tenderness (Dibbets and van der Weele 1996; Ferreira et al. 2016).

Different conservative and surgical protocols have been extensively tested in an attempt to treat TMDs. Nonsurgical methods include anti-inflammatory drugs, occlusal splints, physiotherapy, laser application, and acupuncture. Injection of anti-inflammatory drugs (i.e., corticosteroids) or lubricating materials (i.e., hyaluronic acid [HA]) with or without arthrocentesis or arthroscopic surgeries have been found to reduce pain and to enhance masticatory function in TMD patients (Korkmaz et al. 2016; Bouchard et al. 2017; Candirli et al. 2017; Isacsson et al. 2019). Surgical treatment protocols such as arthrocentesis, arthroscopy, disc surgeries, arthroplasty, and even total joint replacement are used in patients who do not respond to nonsurgical therapies. Arthrocentesis and arthroscopic surgeries are commonly used surgical techniques, particularly for treatment of TMJ disc displacement and osteoarthritis (Nitzan et al. 2017; Hossameldin and McCain 2018).

Platelet concentrates (PCs) are biological autologous products derived from a patient's whole blood. They include platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and plasma rich in growth factors (PRGF). They contain high concentrations of growth factors (GFs) and cytokines that have anti-inflammatory effects and healing enhancing properties. Accordingly, PCs have multiple applications in dento-alveolar, plastic, maxillofacial, and orthopedic surgeries (Floryan and Berghoff 2004; Al-Hamed et al. 2017; Badran et al. 2018; Al-Hamed et al. 2019). In addition, PCs have been used alone or as an adjunct for treatment of TMD patients and were reported to reduce pain and enhance function in such patients (Hegab et al. 2015).

TMDs are considered chronic degenerative conditions in most of cases, therefore treatment protocols based on regenerative medicine that include injections of PCs rich in GFs may enhance the healing process. To date, there is no evidence summarizing the role of PCs in the management of TMDs, so this systematic review and meta-analysis was designed to answer the following question: in patients with temporomandibular joint osteoarthritis or disc displacement, does PC injection reduce pain and improve mouth opening compared to HA or saline/Ringer's solution injections?

Methods

This systematic review was done following the PRISMA guidelines for systematic reviews and meta-analyses (Liberati et al. 2009).

PICO question:

Participants (P): Patients with temporomandibular joint osteoarthritis or disc displacement.

Intervention (I): PC injection with/without arthrocentesis or arthroscopy.

Comparison (C): HA or saline/Ringer's solution injections, with/without arthrocentesis or arthroscopy.

Outcomes (O): Primary outcome: pain. Secondary outcomes: maximum mouth opening (MMO), joint sound, jaw movements, and masticatory efficacy.

Study design: Randomized clinical trials (RCTs).

Search Strategy

A comprehensive electronic search was conducted using the following databases: PubMed, Cochrane Central Register of Controlled Trials, and Scopus. The final search was updated on March 6, 2020. In addition, the online databases of Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery, Journal of Oral Rehabilitation, Journal of Oral and Facial Pain and Headache, and Journal of Craniomaxillofacial Surgery were searched. The reference lists of pertinent reviews on the subject were checked for possible additional studies. The search was performed by 2 researchers without time restriction by using a combination of the following Mesh terms and free text words: "platelet concentrates" OR "Platelet-Rich Plasma"[Mesh] OR "PRP" OR "platelet rich fibrin" OR "PRF" OR "platelet rich in growth factors" OR "PRGF" AND "temporomandibular disorders" OR "Temporomandibular Joint Disorders"[Mesh] OR "Osteoarthritis"[Mesh] OR "disc displacement" OR "internal derangement" OR "Joint Dislocations"[Mesh].

Study Selection

Inclusion criteria: RCTs that evaluated the efficacy of PC injection in treatment of TMJ OA or disc displacement compared to HA or saline/Ringer's solution injections, with/without arthrocentesis or arthroscopy were included. Only English publications were included in this systematic review.

Exclusion criteria: Case reports, case series, observational studies, noncomparative studies, animal studies, reviews, and editorials.

Two independent evaluators (F.S.A. and A.H.) conducted the literature search and screened the articles. If agreement was not achieved, a third researcher (Q.G.) resolved the disagreement. Cohen's Kappa was calculated to detect the interrater reliability.

Data Extraction

The following data were collected for each study: author, year, country, study design, mean age, age range, male: female ratio, type of TMDs, type of

platelet concentrates, treatment groups, follow-up period, primary and secondary outcomes. Three independent evaluators (F.S.A., A.H., Q.G.) collected the data.

Meta-Analysis

Studies that used similar measurement tools for pain and MMO scores were included for meta-analysis. We performed subgroup analysis according to the treatment groups (PC versus HA or PC vs saline) and follow-up time (studies were pooled for 3 mo, 6 mo, and 12 mo). Due to high heterogeneity between studies, a random effect model was used. As pain and MMO are continuous variables, the mean differences for each outcome was calculated. The heterogeneity was assessed using I^2 scores, which were used to assess the proportion of variation between study groups. The I^2 values that ranged from 0% to 100% were interpreted as follows: 25% (low heterogeneity), 50% (moderate heterogeneity), and ≥75% (high heterogeneity) (Higgins et al. 2003).

Critical Appraisal

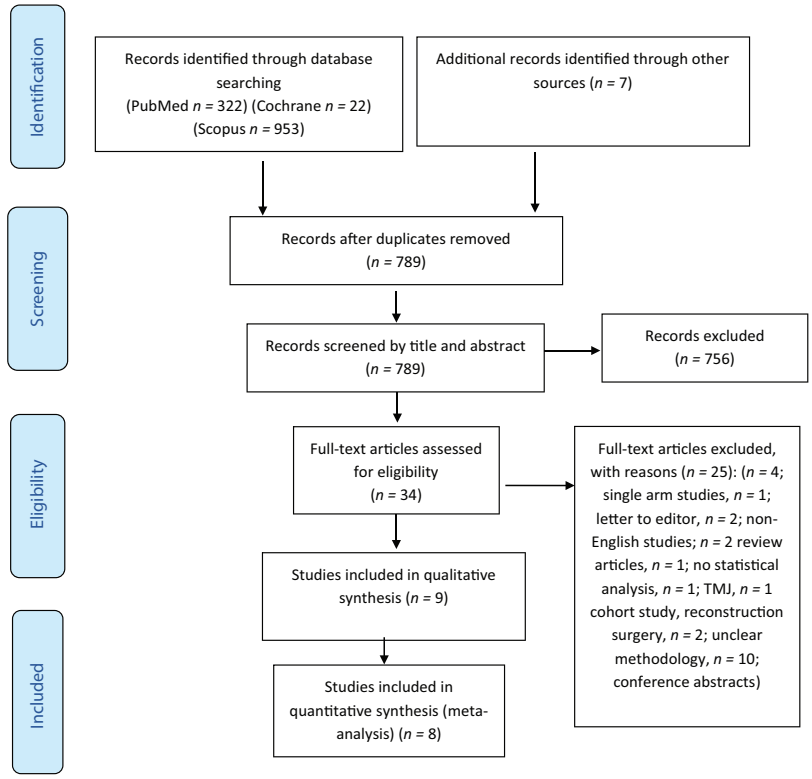
Quality assessment of the included studies was performed following the guidelines of the Effective Public Health Practice Project (EPHPP) quality assessment tool (Armijo-Olivo et al. 2012). This tool has 6 domains: selection bias, study design, confounding factors, blinding, data collection method, withdrawals, and dropout rate. Global overall rating for each study was determined as follows: a) the study is considered strong if no domain is weak and at least half of the domains are strong, b) the study is considered moderate if 1 section is weak, and c) the study is considered weak if ≥2 sections are considered weak.

Results

Study Selection

The electronic and manual searches identified 1,304 articles, of which 515 were excluded because of duplication.

Figure 1. Flowchart of the selection process.



The remaining 789 articles were screened by title and abstract, of which 755 articles were excluded as they did not fit the inclusion criteria. The full text of the related studies was read by 2 researchers for potential inclusion. Of the 34 full-text studies reviewed, 9 studies met the inclusion criteria (Machon et al. 2013; Comert Kilic et al. 2015; Hanci et al. 2015; Hegab et al. 2015; Comert Kilic and Gungormus 2016; Fernandez Sanroman et al. 2016; Fernandez-Ferro et al. 2017; Singh et al. 2019; Toameh et al. 2019). The other 25 articles were excluded as they did not meet the inclusion criteria. The Kappa value was 0.85 which indicates a strong agreement between evaluators (Fig. 1).

Characteristics of Included Studies

Nine RCTs were included in this systematic review (Machon et al. 2013; Comert Kilic et al. 2015; Hanci et al. 2015; Hegab et al. 2015; Comert Kilic and Gungormus 2016; Fernandez Sanroman et al. 2016; Fernandez-Ferro et al. 2017; Singh et al. 2019; Toameh et al. 2019). The total number of included participants was 407 patients. The total numbers of joints were 262, 112, and 112 in the PC, HA, and saline/Ringer's groups, respectively. There were 67 males and 340 females, with ages ranging from 16 to 73 y. Regarding the type of TMJ disease, 4 studies assessed OA, 2 studies assessed OA and disc displacement, and 3 studies assessed disc displacement. Regarding the type of PCs; 7 studies used PRP injections and 2 studies used PRGF. The volume of injected PCs ranged from 0.6 mL to 8 mL with a frequency of 1 to 5 times. The overall follow-up time ranged from 3 to 24 mo (Tables 1 and 2).

The meta-analysis was performed for 2 outcomes; pain and MMO that were assessed in 8 studies. Masticatory efficacy, joint sounds, and jaw movements were assessed only in 3 studies using different

Table 1.
Main Characteristics of Included Studies.

Author, Year	Country	Study Design	M-F Ratio	Age, Mean (SD) (Range), y	TMJ Disease	Total Sample Size	Study Groups		
							PC (No. of Joints)	HA (No. of Joints)	Saline (No. of Joints)
Machon et al., 2013	Czech Republic	Pilot RCT	3:27	33.4 (2.0) (17–65)	OA	30	10	10	10
Hanci et al., 2015	Turkey	RCT	5:15	26.3 (9.3) NR	DDwR	20	17	NA	15
Comert Kilic et al., 2015	Turkey	RCT	3:27	33.37 (14.43) 16–73	OA	30	32	NA	15
Hegab et al., 2015	Egypt	RCT	21:29	38.6 (NR) (31–49)	OA	50	25	25	NA
Fernandez Sanroman et al., 2016	Spain	RCT	6:86	35.8 (NR) (17–67)	DDwoR and OA	92	42	NA	50
Comert Kilic and Gungormus., 2016	Turkey	RCT	5:26	30.48 (13.04) (NR)	OA	31	32	17	NA
Fernandez-Ferro et al., 2017	Spain	RCT	12:88	35.5 (NR) (18–77)	DDwR/ DDwoR and OA	100	50	50	NA
Toameh et al., 2019	Syria	RCT	6:24	38.87 (6.40) (NR)	DDwoR	30	10	10	10
Singh et al., 2019	India	RCT	6:18	35.58 (10.75)	DDwR	24	12	NA	12

DDwoR, disc displacement without reduction; DDwR, disc displacement with reduction; HA, hyaluronic acid; NA, not applicable; NR, not reported; OA, osteoarthritis; PC, platelet concentrate; RCT, randomized clinical trial; TMJ, temporomandibular joint.

measurement tools and follow-up durations, which rendered pooling their data together unfeasible. Furthermore, due to the small number of studies included in the meta-analysis (less than 10 studies), we were unable to assess publication bias by testing funnel plot asymmetry as with fewer studies the test power is low to distinguish between chance and real asymmetry (Ahmed et al. 2012).

Quality Assessment of Included Studies

The Effective Public Health Practice Project (EPHPP) quality assessment tool was used to assess the risk of bias in the included studies. Overall, 4 studies were considered to have strong quality, 4 studies were considered to have moderate quality, and 1 study was considered to have weak quality. However, in the assessment of the blinding section, 5 studies were considered weak, which indicates that the patients, and/or the investigators were aware of treatment groups and this may introduce bias. No protocol in any of the studies was found to evaluate other potential biases. In the case when additional information was required, the authors were contacted, and their responses were considered in the critical appraisal (Table 3).

Pain Scores within the Included Studies

Pain scores were assessed using the visual analog scale (VAS) in all studies. When pre- and posttreatment readings were compared, PCs, HA, or saline injection were found to reduce pain scores in all studies. Four out of 5 studies found a significant difference favoring the use of PC versus HA injections. Three out of 5 studies found a significant difference favoring the use of PC versus saline/Ringer's solution injections. The

Table 2.
Methodology Table.

	Intervention				Comparator			
Author, Year	Treatment Type	Dose	Frequency	Application	Type	Dose	Frequency	Follow-up, mo
Machon et al., 2013	PRP	1 mL	Twice/2 wk intervals	Intraarticular injection	Sodium hyaluronate	1 mL	Twice/2 wk interval	3
Hanci et al., 2015	Arthrocentesis and PRP	0.6 mL	Once	Intraarticular injection	Arthrocentesis and Ringer's solution	NR	Once	6
Comert Kilic et al., 2015	Arthrocentesis and PRP	1 mL	4 times/30 d interval	Intraarticular injection	Arthrocentesis and Ringer's solution	NR	Once	12
Hegab et al., 2015	Arthrocentesis with PRP	1 mL	3 times/ once per wk	Intraarticular injection	Arthrocentesis with HA 20 mg/2 mL	1 mL	3 times/ once per wk	12
Fernandez Sanroman et al., 2016	Arthroscopy with PRGF	8 mL	Once	Intraarticular injection (5 mL in the intermediate joint space and 3 mL in the superior space)	Arthroscopy with saline	NR	Once	24
Comert Kilic and Gungormus., 2016	Arthrocentesis with PRP	1 mL	4 times (once every 3 mo)	0.5 mL intraarticular around the capsule	Arthrocentesis with HA	1 mL	Once after arthro-centesis	12
Fernandez-Ferro et al., 2017	Arthroscopy with PRGF	5 mL	5 times (monthly)	4 mL was injected in superior joint space and 1 mL in inferior joint space	Arthroscopy with 1% Sodium Hyaluronate HA	NR	Once after arthroscopy	18
Toameh et al., 2019	Arthrocentesis with PRP	1 mL	Once	1 mL of PRP intraarticular injections	Arthrocentesis with HA or arthrocentesis (Ringer's solution)	1 mL of HA or 100 mL of Ringer's solution	Once	9
Singh et al., 2019	Arthrocentesis with PRP	1 mL	Once	1 mL of PRP was injected into the joint space	Arthrocentesis with Ringer's solution	100 mL	Once	6

HA, hyaluronic acid; NR, not reported; PRGF, plasma rich in growth factors; PRP, platelet rich plasma.

meta-analyses showed significantly lower pain scores with PC than with HA at 3-mo follow-ups, (average difference = –1.11 [95% CI, –1.62 to –0.60]; $P < 0.0001$), but differences between the 2 groups were not significant at 12-mo follow-up (average difference = –0.57 [95% CI, –1.55 to 0.41]; $P = 0.26$, random-effect model). Also, the average decrease in pain scores with PCs was –1.33 (–2.61 to –0.06), –2.07 (–3.46 to –0.69), –2.71 (–4.69 to –0.72), $P = 0.04$, 0.003, 0.008, compared to saline injection after 3, 6, and 12-mo follow-up respectively (Fig. 2, Appendix Table 1).

Maximum Mouth Opening within the Included Studies

MMO was measured in all studies. MMO was calculated by measuring the distance between the upper and lower central incisors, during nonforced MMO. Only 2 out of 9 studies showed significant improvement in MMO in PC group compared to HA (Hegab et al. 2015) or saline (Toameh et al. 2019) injections. The meta-analysis results showed nonsignificant difference between the PC group compared to HA at 3- and 12-mo follow-up, respectively [weighted mean difference (WMD), 0.97 (–0.68 to 2.63; $P = 0.25$), 0.23 (–3.53 to 3.99; $P = 0.91$) [random-effect model]]. PCs significantly improved MMO scores compared with saline/Ringer's solution injection after 3- and 6-mo follow-up (WMD, 2.9 (1.47 to 4.3), 1.69 (0.13 to 3.25); $P < 0.0001$ and 0.03 respectively, [random-effect model]), whereas there

Table 3.
Quality Assessment of the Included Studies.

Study	Selection Bias	Study Design	Con-founders	Blinding	Data Collection Method	Withdrawals and Dropout Rate	Global Overall Ratings
Machon et al. 2013	Moderate	Strong	strong	Weak	Strong	Strong	Moderate
Hanci et al. 2015	Strong	Strong	Strong	Weak	Strong	Strong	Moderate
Comert Kilic et al. 2015	Strong	Strong	Strong	Moderate	Strong	Strong	Strong
Hegab et al. 2015	Strong	Strong	Strong	Moderate	Strong	Strong	Strong
Fernandez Sanroman et al. 2016	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Comert Kilic and Gungormus., 2016	Strong	Strong	Strong	weak	Strong	Strong	Moderate
Fernandez-Ferro et al. 2017	Strong	Strong	Strong	Moderate	Strong	Strong	Strong
Toameh et al. 2019	Moderate	Strong	Moderate	Weak	Strong	Strong	Moderate
Singh et al. 2019	Strong	Strong	Weak	Weak	Strong	Strong	Weak

was no differences after 12 mo (WMD, 0.51 (–0.95 to 1.96); $P = 0.49$) (Fig. 3, Appendix Table 2).

Jaw Movements within the Included Studies

Lateral and protrusive jaw movements were assessed in 2 studies (Comert Kilic et al. 2015; Comert Kilic and Gungormus 2016) that assessed the treatment of TMJ OA using arthrocentesis with PRP versus arthrocentesis alone (Comert Kilic et al. 2015) or arthrocentesis with HA (Comert Kilic and Gungormus 2016). PRP significantly improves the lateral jaw movement, when comparing the baseline versus the posttreatment readings, but its efficacy was not significantly better than the comparator groups (arthrocentesis with/without HA) (Comert Kilic et al. 2015).

Joint Sounds within the Included Studies

Joint sounds were assessed in 6 studies using different scales of measurement: VAS scores, audio recorder, research diagnostic criteria for TMD (RDC/TMD) questionnaire, self-reported by patients, doctor examination, or combinations. There was no significant difference between different treatment groups.

Masticatory Efficacy within the Included Studies

Three publications assessed masticatory efficacy (Comert Kilic et al. 2015; Comert Kilic and Gungormus 2016; Toameh et al. 2019). This was done using VAS in which patients were asked to select a value on a 0–10 cm line scale, which corresponded to their perception. Masticatory efficacy was defined by scores ranging from 0, which indicated reduced masticatory efficacy or chewing liquid food, to 10, which meant excellent masticatory efficacy or chewing hard food. Two studies showed significant improvement in masticatory function by the combination of arthrocentesis with PRP compared to arthrocentesis alone (Comert Kilic et al. 2015) or arthrocentesis with HA (Toameh et al. 2019). However, 1 study found nonbeneficial effect in masticatory function in PRP group compared with HA group (Comert Kilic and Gungormus 2016).

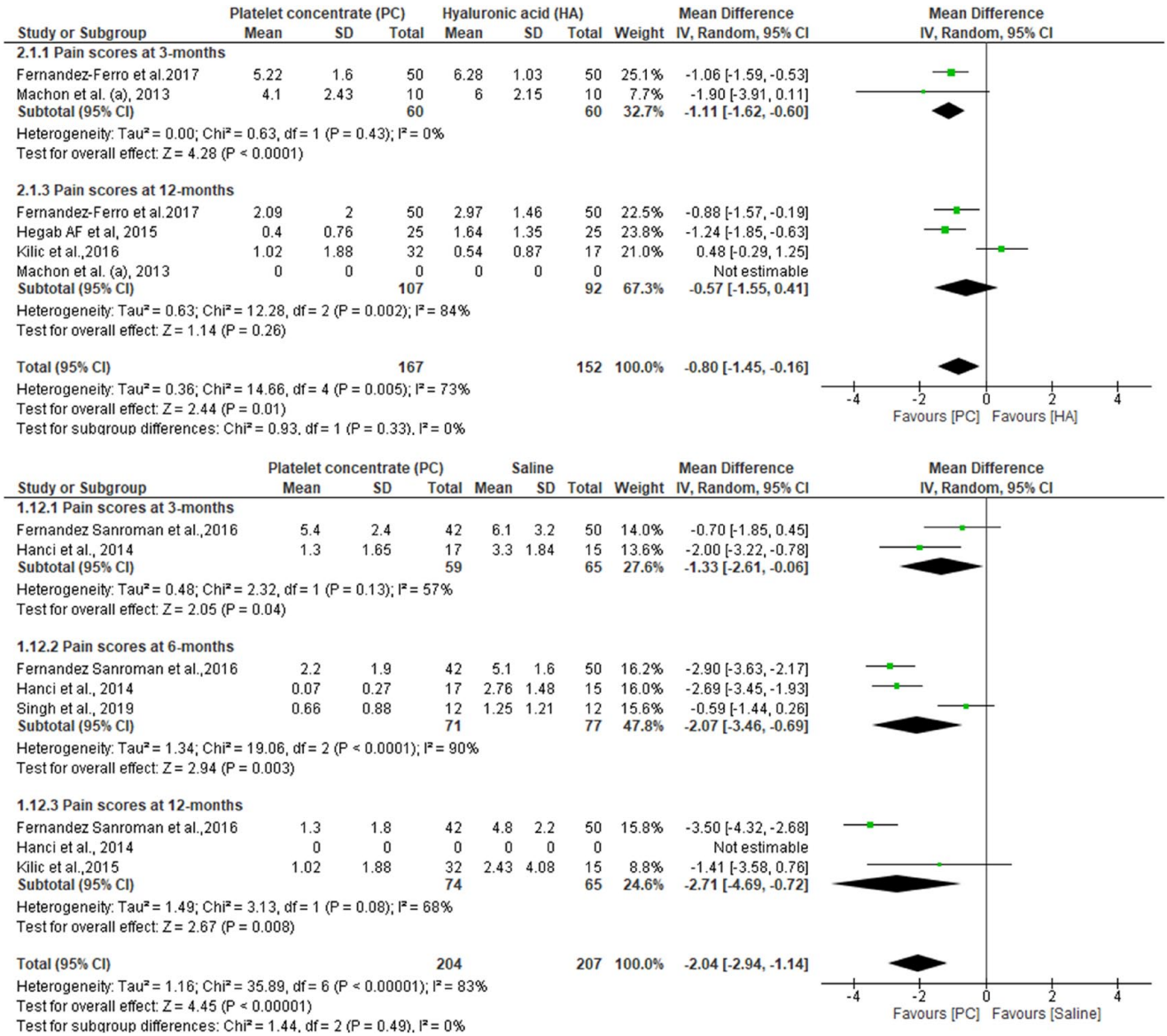
Properties of Platelet Concentrates

Different protocols for preparation of platelet concentrates were used. PRP was used in 7 studies and PRGF was used in 2 studies, although they were different in terms of preparation protocols; single versus 2 spin protocols, blood volume, speed, and time as well as different activation materials. No analysis of platelet or growth factor concentrations was reported within the included studies. Activation materials such as calcium chloride and thrombin were used to activate platelets and to allow the release of GFs. In this systematic review, 3 studies used calcium chloride to activate the PCs, 1 study used photoactivation, 4 studies used no activation method, and 2 studies did not report on PC activation. The included studies used different volumes of platelet concentrates, ranging from 0.6 to 8 mL. PCs were injected once in 4 studies, 2 times in 1 study, 3 times in 1 study, 4 times in 2 studies, and 5 times in 1 study. The timing was weekly, monthly, and every 3 m, for a maximum duration of 1 y (Appendix Table 3).

Discussion

In this systematic review and meta-analysis, we analyzed the available clinical studies regarding the role of PCs in terms of pain reduction and MMO scores in patients with TMJ OA or disc displacement. The main findings of this review are that PC injection seems to reduce pain compared to HA (at 3-m

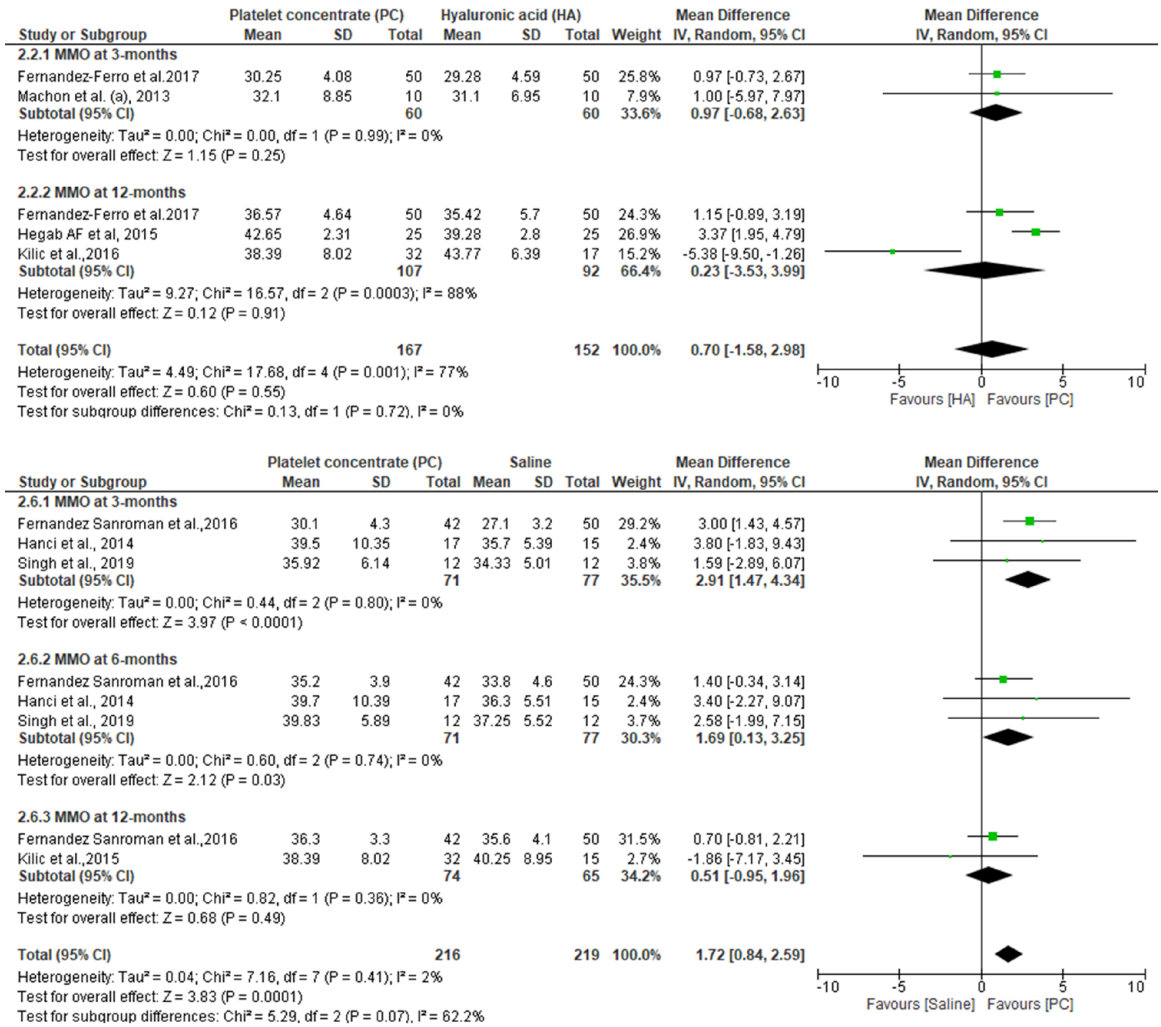
Figure 2. Pain scores in platelet concentrate (PC) group versus hyaluronic acid (HA) or saline injections.



follow-up) or saline injections (at 3, 6, and 12-mo follow-up).

The positive role of PCs in pain control was reported in many studies in oral surgery (Al-Hamed et al. 2019), musculoskeletal (Balasubramaniam et al. 2015), and knee osteoarthritis (Laudy et al. 2015). PC may cause immunomodulation effects. PC induces considerable changes in the level of proinflammatory mediators such as an increased level of Lipoxin A4 and thus suggests that PCs could prohibit cytokine secretion, reduce inflammation, and promote tissue healing (El-Sharkawy et al. 2007). Furthermore, PCs secrete a collection of bioactive molecules (i.e., GFs) that have an essential role in inflammation, cell movement, and metabolism. Their anti-inflammatory effects occur via the canonical pathway of nuclear factor kB signaling in different cell types including macrophages, synoviocytes, and chondrocytes. Joint cells also secrete additional active molecules in response to PC injection, and this may result in enhancing angiogenesis, anabolism, and recruitment of repairing cells to the joint spaces (Andia and Maffulli 2013). As PCs secrete their contents within 2 wk after activation (Dohan Ehrenfest et al. 2018) and most PC injections were performed during the first 3 mo of treatment, thus this could explain the better outcomes of PC during the 3-mo follow-up only compared to HA. However, HA provides prolonged anti-inflammatory and lubrication effects (Bowman et al. 2018), and this could explain the comparable effects between PC and HA groups at 12 mo follow-up.

Figure 3. Maximum mouth opening (MMO) in platelet concentrate (PC) group versus hyaluronic acid (HA) or saline/Ringer's solution injections.



The meta-analysis of MMO results showed that PC achieved better outcomes than saline injections for the first 6 mo, however, no significant differences compared to HA were observed. HA is a physiological material secreted by synovial cells in the TMJ that enhances joint movement due to its lubricating and anti-inflammatory properties (Bowman et al. 2018). Osteoarthritic patients tend to have a reduced concentration of intraarticular HA as a result of depolymerization of oxygen and accumulation of acid molecules (Triantaffilidou et al. 2013). The lubricating effect of HA may be the reason of improvement in MMO in the HA group. In agreement with these findings, HA was reported to promote long-term joint lubrication and to enhance joint movement (Alpaslan and Alpaslan 2001). However, the effect of PC lasts for a shorter period (Dohan Ehrenfest et al. 2018), thus a regular PC injection could preserve a stable amount of anti-inflammatory and healing inducing GFs and could result in prolonged effect.

However, the meta-analysis results showed significant improvement in pain scores in PC compared to HA or saline groups. The average reduction in pain scores after 3 mo was small (around 10% and 13%, respectively) and this could raise the issue of whether they are clinically relevant. In addition, the average increase in mouth opening in PC was very small (0.97 mm and 2.91 mm) compared to HA and saline treatments respectively.

Concerning joint sounds, controversial results were reported regarding the efficacy of PC over other treatment modalities. This could be explained by the different measurement tools that were used in different studies such as VAS scores, audio recorder, RDC/TMD questionnaire or by stethoscope. Both VAS scores and RDC/TMD questionnaire are subjective in nature, whereas recording audio or using a stethoscope may be more accurate compared to other methods. In addition, joint sounds are different among

patients and could indicate the disease progression (e.g., clicking is an indicator of disc displacement with reduction, and crepitus is an indicator of disc displacement without reduction) (Prinz 1998; Ogutcen-Toller 2003).

The total male:female ratio was 67:340. Females were 5.07 times more exposed to TMDs than males. This high prevalence of gender-based distribution of patients with TMDs was also reported in other studies (Bagis et al. 2012; Schmid-Schwap et al. 2013). Hormonal changes and stress may contribute to the increased rate of female/male ratio of patients with TMJ-diseases (Gus et al. 2015; Kim et al. 2015).

The included studies used different protocols for preparation of PRP or PRGF. In addition, no study reported a quantitative analysis of the composition of PCs. Furthermore, no complete description of PRP protocols in previous clinical studies were reported (Chahla et al. 2017). This may explain the inconsistency among different studies. Therefore, a precise description of PC preparation protocols and its compositional analysis are required to allow comparison and reproducibility of studies.

The main limitations of the available evidence were the heterogeneity and low number of included studies that make it hard to draw a conclusion. This study includes 2 types of TMJ disorders; disc displacement and OA as both diseases have common similar symptoms and treatment protocols. Furthermore, this review did not include non-English studies, that might have useful information regarding the role of platelet concentrates in the treatment of TMDs.

Conclusion

In management of patients with disc displacement or osteoarthritis, PC seems to reduce pain scores compared to HA (for the first 3 mo only), whereas it reduces pain and increases MMO for longer duration compared to saline. However, due to high heterogeneity and different PC preparation protocols, these findings should be carefully interpreted, and further prospective RCTs are required.

Author Contributions

F.S. Al-Hamed, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; A.H. Hijazi, contributed to conception, design, data acquisition, and interpretation, critically revised the manuscript; Q. Gao, contributed to data acquisition, critically revised the manuscript; Z. Badran, F. Tamimi, contributed to conception and design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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