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Review

Is the application of platelet concentrates effective in the prevention and treatment of medication-related osteonecrosis of the jaw? A systematic review

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ABSTRACT

The aim of this systematic review was to answer the question: Is the application of autologous platelet concentrates (APCs) effective in the prevention and treatment of medication-related osteonecrosis of the jaw (MRONJ)? A literature search of PubMed, Scopus, and Web of Science databases (articles published until June 30, 2019) was conducted, in accordance with the PRISMA statement, using search terms related to "platelet concentrate" and "osteonecrosis". The Jadad scale was used to assess the quality of the articles. Fisher's exact test was used to evaluate eventual differences between groups.

Of 594 articles, 43 were included in the review (8 for MRONJ prevention and 35 for MRONJ treatment). Out of a total of 1219 dental extractions recorded (786 with APCs), only 12 cases of MRONJ have been reported (1%), all in patients with a history of high-dose antiresorptive treatment, and regardless of the use of APCs ($p = 0.7634$). Regarding MRONJ treatment, there were no statistically significant differences in terms of improvement between APC application and surgical treatment alone ($p = 0.0788$).

Results are not sufficient to establish the effectiveness of APCs in the prevention and treatment of MRONJ. Randomized controlled trials with large sample size are needed.

1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is an infectious complication of bone antiresorptive drug therapies (bisphosphonates or denosumab) or anti-angiogenic treatment for cancer, defined as a persistent bone exposure within the oral cavity (or bone that can be probed through a fistula) for a minimum period of eight weeks and a progressive involvement of the jaws, occurring in patients who have received these drugs without a history of radiotherapy in the head and neck region (Ruggiero et al., 2014).

In a recent meeting, a group of researchers of the Workshop of European Task Force on MRONJ proposed a revision of American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria and classification, suggesting that "patients presenting with non-exposed MRONJ without fistulas (e.g., dentally unexplained pain, mobile teeth not due to periodontitis, numbness of the lip, mandibular fracture) continue to remain excluded from MRONJ case definition" and that "the requirement of 8-week observation of potential MRONJ manifestation to fit the case definition may no longer be necessary" (Schiodt et al., 2019).

The pathophysiology of MRONJ has not been clearly elucidated, but the principal evidence-based mechanisms of pathogenesis include altered bone remodeling, lack of immune resiliency, soft-tissue toxicity, infectious/inflammatory processes, and altered angiogenesis (Chang et al., 2018).

Prevention and control of the risk factors are fundamental to avoid osteonecrosis of the jaws. MRONJ may develop spontaneously or can be induced by invasive dental procedures (Diniz-Freitas et al., 2016).

Recently, Schiodt et al. stated that "tooth extraction does not automatically translate into an increased risk of developing MRONJ, as certain surgical procedures notably reduce the risk" and "the high risk of developing MRONJ after tooth extraction might be related to an underlying pre-existing dental/periodontal infection

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rather than to the surgery per se" (Schiodt et al., 2019). These statements are also supported by recent animal model studies (Poubel et al., 2018; Bolette et al., 2019).

Complementary treatments, including laser treatment, ozone-therapy, and autologous platelet concentrates (APCs), are being developed and studied to improve healing in both the prevention and treatment of MRONJ (Del Fabbro et al., 2015; Lopez-Jornet et al., 2016; Diniz-Freitas and Limeres 2016; Di Fede et al., 2018).

Although antiresorptive drugs have a target effect on bone tissue, the loss of oral mucosa in almost every patient with MRONJ suggests an adverse effect also on epithelial tissues. This could play a role in wound healing in patients receiving these drugs (Yuan et al., 2019).

Autologous platelet concentrates have been used in medicine and dentistry for regenerative procedures and seem mainly to promote soft-tissue wound healing by delivering more than natural concentrations of autologous growth factors (Miron et al., 2017).

However, the efficacy of platelet concentrates used as surgical adjuvant to improve healing and promote tissue regeneration is at the center of a recent academic debate (Giudice et al., 2019).

More than a decade has passed since the publication of the first studies describing the use of APCs, and their possible positive effect, in the treatment and prevention of MRONJ (Curi et al., 2007; Torres et al., 2008). The use of different APCs, such as platelet-rich plasma (PRP), plasma-rich growth factors (PRGF), and platelet-rich fibrin (PRF), have been described in this decade (Del Fabbro et al., 2015; Lopez-Jornet et al., 2016).

The main objective of this study was to conduct a systematic review of the literature to determine whether the application of platelet concentrates is effective in the prevention and treatment of MRONJ and to consider the possible role of APCs in triggering angiogenesis and regulating healing processes.

2. Material and Methods

The authors followed criteria established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this review (Liberati et al., 2009).

2.1. PICO question

Is the application of platelet concentrates effective in the prevention and treatment of medication-related osteonecrosis of the jaw compared to procedures in which they are not used?

2.2. Search strategy

An electronic literature search was performed using the following databases: Medline (using PubMed), Scopus, and Web of Science. Articles published up to June 30, 2019, were included. The keywords used were "platelet concentrate" and "osteonecrosis". Another search in Medline was performed using a specific query, considering also the nomenclature of the different platelet concentrates (Table 1).

2.3. Inclusion and exclusion criteria

The following inclusion criteria were applied: (1) any original publication in the English language, (2) studies conducted in humans, (3) patients with diagnosis of MRONJ (in accordance with AAOMS or American Society of Bone and Mineral Research [ASBMR] definitions) in treatment with antiresorptive or anti-angiogenic drugs for metabolic diseases or malignancy related to MRONJ, (4) use of autologous platelet concentrates, and (5) outcome variables mentioned and reported in the publication.

The following exclusion criteria were applied: (1) in vitro studies; (2) experimental animal studies; (3) literature reviews, letters, editorials, doctoral theses, or abstracts; and (4) patients with osteoradionecrosis of the jaws.

The reference list of review articles was analyzed to search for other articles not found in the electronic literature search.

2.4. Selection of the studies

The manuscripts selected included case reports, case series, prospective clinical trials, nonrandomized and randomized studies, and observational studies. Two authors (CB, FB) conducted database searches independently, and discrepancies were resolved in a consensus meeting with a third reviewer (AG).

2.5. Data extraction

Data was extracted by two reviewers independently (CB, FB). Disagreement was subject to a new evaluation with a third reviewer (LF). The studies were divided according to the type of intervention (prevention, treatment) and the type of platelet concentrate used (PRP, PRGF, or PRF).

The variables extracted from the studies were the following: study design, sample size, gender, age, comorbidities, jaw receiving the treatment (maxilla and/or mandible), reason, type, dosage and duration of antiresorptive therapy, outcome variables (including recurrences and complications), follow-up duration. For treatment studies, we also extracted, when present, the stage of the lesions. For prevention studies, we extracted the type of procedure (tooth extraction or implant surgery).

2.6. Data analysis

Data in the included studies was analyzed with descriptive statistics: total number of cases, percentage of outcome variables, distribution of sex and age, and so on. Data was subdivided by type of intervention and platelet concentrate used.

Outcome variables of MRONJ treatment studies were classified into three categories: "complete response," "partial response," and

Table 1
Detailed search string - Medline.

((“autologous platelet concentrates” [All Fields] OR “autologous platelet concentrate” [All Fields]) AND (“osteonecrosis” [All Fields] OR “osteonecrosis of the jaw” [All Fields] OR “bone necrosis” [All Fields] OR “jaw necrosis” [All Fields] OR “ONJ” [All Fields] OR “BRONJ” [All Fields] OR “MRONJ” [All Fields]) OR “ARONJ” [All Fields])) OR ((“platelet concentrates” [All Fields] OR “platelet concentrate” [All Fields]) AND (“osteonecrosis” [All Fields] OR “osteonecrosis of the jaw” [All Fields] OR “bone necrosis” [All Fields] OR “jaw necrosis” [All Fields] OR “ONJ” [All Fields] OR “BRONJ” [All Fields] OR “MRONJ” [All Fields]) OR “ARONJ” [All Fields])) OR ((“platelet-rich plasma” [All Fields] OR “PRP” [All Fields]) AND (“osteonecrosis” [All Fields] OR “osteonecrosis of the jaw” [All Fields] OR “bone necrosis” [All Fields] OR “jaw necrosis” [All Fields] OR “ONJ” [All Fields] OR “BRONJ” [All Fields] OR “MRONJ” [All Fields]) OR “ARONJ” [All Fields])) OR ((“platelet-rich fibrin” [All Fields] OR “PRF” [All Fields]) AND (“osteonecrosis” [All Fields] OR “osteonecrosis of the jaw” [All Fields] OR “bone necrosis” [All Fields] OR “jaw necrosis” [All Fields] OR “ONJ” [All Fields] OR “BRONJ” [All Fields] OR “MRONJ” [All Fields]) OR “ARONJ” [All Fields])) OR ((“plasma rich in growth factors” [All Fields] OR “PRGF” [All Fields]) AND (“osteonecrosis” [All Fields] OR “osteonecrosis of the jaw” [All Fields] OR “bone necrosis” [All Fields] OR “jaw necrosis” [All Fields] OR “ONJ” [All Fields] OR “BRONJ” [All Fields] OR “MRONJ” [All Fields]) OR “ARONJ” [All Fields])) OR ((“concentrated growth factors” [All Fields] OR “CGF” [All Fields]) AND (“osteonecrosis” [All Fields] OR “osteonecrosis of the jaw” [All Fields] OR “bone necrosis” [All Fields] OR “jaw necrosis” [All Fields] OR “ONJ” [All Fields] OR “BRONJ” [All Fields] OR “MRONJ” [All Fields]) OR “ARONJ” [All Fields]))

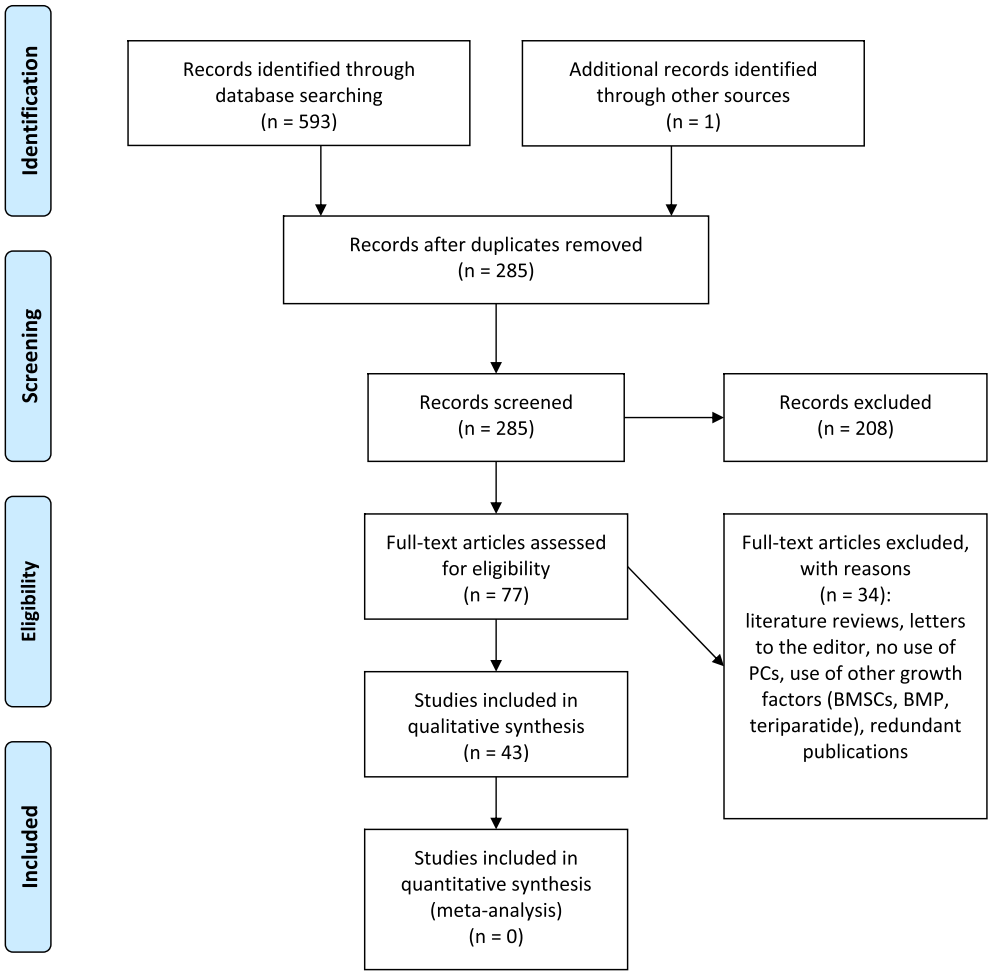

Fig. 1. Prisma flow diagram.

"negative response," according to authors' descriptions in the articles examined; partial response meant an improvement of the disease (stage and quality of life) without complete mucosal coverage of the exposed bone.

Clinical trials comparing APCs with traditional intervention were evaluated with the Jadad scale (Jadad et al., 1996) before being included in the meta-analysis; papers with a Jadad score of 3 or less were excluded from quantitative synthesis.

The significance of the relationship between the application of APCs and healing or improvement of the disease was assessed with Fisher's exact test to evaluate eventual differences between the two surgical protocols. The level of significance was set at $P < .05$. Statistical analysis was performed by using the STATA software program (STATA, Release 14; STATA Corporation, College Station, TX).

3. Results

The results of the literature search are presented in the PRISMA flow diagram (Fig. 1).

3.1. Study selection

The search strategy yielded 593 records (157 from PubMed, 172 from Scopus, 136 from Web of Science, and 128 from the specific query on Medline); one additional article was identified through a hand search of the reference list of review articles. After removal of duplicates, 285 records remained. After title and abstract screening, 77 articles were identified for full-text retrieval and analysis. Of these, 34 did not meet the inclusion criteria (literature reviews, letters to the editor, no use of PCs, use of growth factors, redundant publications). The remaining 43 articles were included in the systematic review; the included papers are listed in Table 2 according to study design, type of intervention, and platelet concentrate used.

3.2. MRONJ prevention studies

Eight studies related to APCs used for MRONJ prevention were included: two case reports, one case series, one retrospective study, two prospective studies, two clinical trials. All the data concerning the studies is reported in Tables 3 and 4. No side effects were reported. Five studies reported the role of APCs as a preventive measure in patients requiring dental extractions: 262 patients received APCs (786 extractions) and 158 patients were recruited as controls (433 extractions). MRONJ was reported for 12 sites: seven in the APC group (0.9%) and five in the control group (1.2%). A delayed recovery with bone exposure was reported for nine patients (12 extractions) in the control group (2.8%), with complete healing after 12 weeks. Three studies described APCs as a preventive measure in implant surgery: 237 patients received APC during implant surgery (1277 implants placed, 56 procedures of sinus augmentation). No cases of MRONJ were reported in a long follow-up (up to 9 years), but 16 implants (1.3%) were lost in 16 patients (6.8%).

Table 2
Articles included in the systematic review.

Type of intervention	APC	Study design	Number of articles	References
Prevention	PRP	CR	1	Torres et al. (2008)
	PRGF	CR	1	Cucchi et al. (2016)
		R	1	Mozzati et al. (2015)
		P	2	Scoletta et al. (2011, 2013)
		T	1	Mozzati et al. (2012b)
	PRF	CS	1	Vlad et al. (2017)
		T	1	Asaka et al. (2016)
Treatment	PRP	CR	6	Antonini et al. (2010) Bernardi et al. (2018) Cetiner et al. (2009) Curi et al. (2007) Lee et al. (2007) Vairaktaris et al. (2009)
		CS	3	Adornato et al. (2007) Curi et al. (2011) Merigo et al. (2018)
		R	3	Longo et al. (2014) Martins et al. (2012) Mathias Duarte et al. (2013)
		P	2	Bocanegra-Perez et al. (2012) Mauceri et al. (2018)
		T	1	Coviello et al. (2012)
	PRGF	CR	3	Anitua et al. (2013) Garcia-Gil et al. (2019) López et al. (2019)
		R	1	Mozzati et al. (2012a)
	PRF	CR	8	De Castro et al. (2016) Gönen and Yılmaz Asan (2016) Maluf et al. (2016), 2018 Saad D et Saad P (2017) Sahin et al. (2019) Soydan and Uckan (2014) Tsai et al. (2016)
		CS	3	Bilimoria et al. (2017) Inchingolo et al. (2017) Mourão et al. (2019)
		R	2	Valente at al (2019) Dinca et al. (2014)
		P	2	Kim et al. (2014) Nørholt and Hartlev (2016)
		T	1	Giudice et al. (2018b)

CR: case report (up to 4 patients).
CS: case series.
R: retrospective study.
P: prospective study.
T: clinical trials (only perspective study with control group).

Only two studies were set up as clinical trials, all related to dental extractions (Mozzati et al., 2012b; Asaka et al., 2016). The results of evaluation with the Jadad scale (Jadad et al., 1996) are reported in Table 5; both articles reached a score of 1 and were not included in the quantitative synthesis.

The results of the Fisher's exact test to evaluate the significance of the relationship between the application of APCs and prevention of MRONJ after dental extractions, considering all cases screened, showed no differences between the two surgical protocols (Table 6), with $p > .05$ ($p = 0.7634$).

3.3. MRONJ treatment studies

Thirty-five studies related to APC used for MRONJ treatment were included: 17 case reports, six case series, six retrospective studies, four prospective studies, two clinical trials. All the data concerning the studies is reported in Tables 7 and 8. PRF was the most studied platelet concentrate in the treatment for MRONJ (16 articles, instead of 15 on PRP and 4 on PRGF). A total of 410 patients were recruited in the studies considered: 326 underwent surgery with APC application, 52 underwent surgery without APC, and 32 were managed conservatively (not considered). Lesions treated surgically totaled 402: 344 with APC, 58 with bone surgery alone. No side effects were reported.

APC treatment outcome showed complete response in 302 lesions (87.8%), partial response in 23 lesions (6.7%), negative response in 19 lesions (5.5%), considering the clinical evaluations performed at the follow-up visits in a variable range (1–94 months).

Surgery alone treatment outcome showed complete response in 37 lesions (63.8%), partial response in 14 lesions (24.1%), negative response in seven lesions (12.1%).

Only two studies were set up as clinical trials (Coviello et al., 2012; Giudice et al., 2018b). The results of evaluation with the Jadad scale (Jadad et al., 1996) are reported in Table 9: Coviello's article reached a score of 1; Giudice's article reached a score of 3. Neither was included in the quantitative synthesis.

The results of the Fisher's exact test to evaluate the significance of the relationship between the application of APCs and improvement of MRONJ after surgical treatment, considering all cases screened, showed no differences between the two surgical protocols (Table 10), with $p > .05$ ($p = 0.0788$).

4. Discussion

Forty-three articles were included in this systematic review, eight for MRONJ prevention and 35 for MRONJ treatment, for a total of 657 and 410 treated patients, respectively. Results are not sufficient to establish the effectiveness of APCs in the prevention and treatment of MRONJ compared to standard procedures.

Treatment of patients at risk of developing MRONJ or with an active disease aims to preserve the quality of life by controlling pain, managing infection, and preventing the development of new areas of necrosis (Allen and Ruggiero 2014). Healing of soft and hard tissues is compromised by antiresorptive therapies and other habits and/or comorbidities that can affect systemic conditions (Yuan et al., 2019). The lack of epithelization exposes the bone to the oral microbial population, which can result in recurrent and persistent infections (Hallmer et al., 2017).

Several protocols for the prevention of MRONJ have been proposed, including antibiotic prophylaxis, antiseptic rinses, drug holiday, primary closure of the extraction socket, ozone therapy, and use of autologous platelet concentrates (Diniz-Freitas and Limeres 2016; Di Fede et al., 2018).

A conservative approach with antibiotics and local antiseptics is the first choice in the treatment of MRONJ, but usually an additional treatment is needed (Nisi et al., 2018). Other authors have suggested that surgical treatment is also indicated in earlier stages of MRONJ to limit bone removal (Ristow et al., 2019). Defining resection margins appears crucial because the success of surgical treatment seems to be related to the complete removal of necrotic bone (Giudice et al., 2018a; Wehrhan et al., 2019).

It is important to underline that the risk of developing MRONJ and the response to treatment are mainly influenced by the type (bisphosphonates or denosumab) and dose (low or high dose) of drug therapy, in relation to the patient's primary disease (metabolic or malignant) (Ruggiero et al., 2014). Furthermore, the replacement of a bisphosphonate with denosumab is an additional risk factor for the development of MRONJ (Higuchi et al., 2018).

The use of APCs is an intense research topic in oral and maxillofacial surgery. The effectiveness of APCs on wound healing and tissue regeneration is controversial. Several protocols to obtain APC have been developed, but each product is different in potential uses and biology. The three most used are PRP, PRGF, and PRF. PRP and PRGF are first-generation platelet concentrates that

Table 3
General features of the studies on MRONJ prevention.

	Reference	Number of patients	Mean age (range), years	Gender M/F	Primary cause of disease	Drugs administered	Time of drug treatment, months	Comorbidities, other habits/medications
PRP	Torres et al. (2008)	1	64	0/1	Osteoporosis	LD A	72 m (deduced from the text)	–
PRGF	Cucchi et al. (2016)	1	65	1/0	Rheumatoid arthritis	Bisphosphonates	Not reported	Corticosteroids
	Mozzati et al. (2012b)	PRGF: 91 Control: 85	– (44–83)	PRGF 36/55 Control 39/46	PRGF: Prostatic carcinoma 33 Breast carcinoma 17 MM 36 Lung carcinoma 3 Ovarian carcinoma 2 CTR: Prostatic carcinoma 27 Breast carcinoma 34 MM 21 Lung carcinoma 2 Ovarian carcinoma 1	HD Z	4-mg infusion every 21 days	PRGF: Chemotherapy 21 Corticosteroids 47 Smoking 15 Control: Chemotherapy 15 Corticosteroids 58 Smoking 21
	Mozzati et al. (2015)	235	60.7 ± 7.3 (48–79)	0/235	Osteoporosis	LD A 141 I 68 R 45	40.2 ± 18.3	Corticosteroids 24 Diabetes 21 Smoking 51
	Scoletta et al. (2011)	65	64.81 + 10.9 (–)	20/45	Breast cancer 32 MM 21 Osteoporosis 2 Prostate cancer 4 Rheumatoid arthritis 1 Paget's disease 1 Lung cancer 1 Ovarian cancer 1 Rhinopharyx cancer 1	HD P 2 Z 57 Z + P 5	Not reported	Corticosteroids 5
	Scoletta et al. (2013)	63	65.82 ± 8.82 (–)	18/45	Breast cancer 30 Multiple myeloma 20 Osteoporosis 6 Prostate cancer 5 Lymphoma 1 Lung cancer 1	HD Z 54 P 4 LD I 5	16.84 ± 13.95 infusions Patients who were treated with zoledronic acid received 4 mg i.v. over 15 min monthly; patients treated with pamidronate received 90 mg over 1 h i.v. monthly; patients treated with ibandronate received 6 mg by 15-min infusion every 3–4 weeks	Corticosteroids 18
PRF	Asaka et al. (2016)	PRF: 29 Control 73	PRF: 73 (24–87) Control: 68 (33–88)	PRF: 3/26 Control 6/67	PRF Osteoporosis 29 Control Osteoporosis 73	LD PRF A 10 R 12 M 10 E 1 Control A 43 R 37 M 2 E 4	PRF 51 m CTR 31 m	PRF Rheumatoid arthritis 4 Systemic lupus Erythematosus 2 Other autoimmune disease 3 CTR Rheumatoid arthritis 15 Systemic lupus Erythematosus 4 Other autoimmune disease 6
	Vlad et al. (2017)	14	–	3/11	Osteoporosis 2 Breast carcinoma 9 Prostati carcinoma 2 Lung carcinoma 1	(Z, I) Data unclear	12 m: 2 24 m: 3 36 m: 3 >36 m: 6	Not reported

Z = zoledronic acid, P = pamidronic acid, A = alendronic acid, I = ibandronice acid, R = risedronic acid, E = etidronic acid, M = minodronic acid, MM = Multiple Myeloma, i.v. = intravenous administration.

involve the use of and anticoagulant and activator: PRP preparation protocol requires two centrifugation steps. PRGF preparation protocol requires one centrifugation with tubes containing anticoagulant, and the use of calcium chloride to activate the product (Ehrenfest et al., 2009).

In 2001, Choukroun et al. described PRF for the first time; according to legal restrictions on blood handling, Choukroun developed an APC that did not require any manipulation after blood collection and centrifugation, as a substitute for PRP (Choukroun et al., 2001). Ease of preparation, low cost, and outpatient use are unique features of PRF (Fortunato et al., 2018).

Different protocols have been described for preparation of PRF, but the use of trade names such as L-PRF™ (leukocyte and platelet-rich fibrin) and A-PRF™ (advanced platelet-rich fibrin) has confused many authors and readers. Recently Miron et al. proposed the standardization of relative centrifugal forces in preparation protocols in the studies related to PRF, suggesting that the characteristics of the centrifuge should be reported in the text as well as

Table 4
Specific features and outcomes of the studies on MRONJ prevention.

	Reference	Number of sites treated	Sites Mand/Max	Procedure	Type of surgical intervention	Antibiotics	Follow-up	Outcome
PRP	Torres et al. (2008)	6	Mandible and maxilla	Bilateral sinus augmentation and implant surgery (2 stages)	Posterior maxilla augmentation by means of mandibular block bone grafts and the sinus floor augmentation technique, using as bone graft PRP mixture with an inorganic bovine hydroxyapatite (80%) and autogenous bone (20%)	Not reported	4 m, 1 y, 3 y	positive
PRGF	Cucchi et al. (2016)	4	Mandible	Tooth extractions 7 Implants 4	Crestal incision without releasing incisions, full thickness buccal flap + non-traumatic extraction. PRGF application to implant sites and implant surface + PRGF clot membranes and 4 −0 resorbable sutures	Antibiotic Prophylaxis with amoxicillin + clavulanic acid 3 g/day for 6 days, starting with 2 g 1 h before surgery.	12 m	positive
	Mozzati et al. (2012b)	542 PRGF 275 CTR 267	PRGF Mandible 142 Maxilla 133 CTR Mandible 145 Maxilla 122	Tooth extractions	Tooth extractions with intrasulcular incisions and detachment of full thick- ness flaps + PRGF membrane comprised of a plasma fraction poor in growth factors was then placed between the bone tissue and the mucosal flap to promote healing and 4-0 sutures	amoxicillin/clavulanate potassium, at a dosage of 1-g tablet every 8 h for a total of 6 days, starting from the evening before the surgical appointment or erythromycin, at a dosage of 600-mg tablets every 8 h for 6 days, when an allergy to penicillin was declared	24–60 m	5 MRONJ in CTR group (average of 91, 6 days after tooth extraction)
	Mozzati et al. (2015)	1267	Mandible 607 Maxilla 606 Sinus augmentation 54	Implant surgery	Before installation, implants were carefully embedded in liquid PRGF-Endoret with the aim of bioactivating the implant surface. A portion of the PRGF clot could also be flattened and used as a covering membrane before flap closure.	antibiotic prophylaxis with amoxicillin 1 g every 12 h from the day before the surgery and for 5 days thereafter	2-9 y	16 implants lost in 16 patients No cases of MRONJ
	Scoletta et al. (2011)	220	Mandible 113 Maxilla 107	Tooth extraction	Tooth extractions + piezo surgery + PRGF with flap	amoxicillin/clavulanate potassium (1-g tablets every 8 h for 6 days) or eryth- romycin (600-mg tablets every 8 h for 6 days) when an allergy to penicillin was declared.	13.06 ± 1.35 m	MRONJ occurred in 5 post extraction sites (2.27%)
	Scoletta et al. (2013)	202	Mandible 111 Maxilla 91	Tooth extraction	Tooth extractions + piezo surgery + PRGF without flap	amoxicillin/clavulanate potassium (1-g tablets every 8 h for 6 days) erythromycin (600-mg tablets every 8 h for 6 days) in case of allergy to penicillin	1, 3, 6, 12 m	MRONJ in 2 post extraction sites
PRF	Asaka et al. (2016)	PRF 52 CTR 166	PRF Mandible 24 Maxilla 28 CTR Mandible 89 Maxilla 77	Tooth extraction	Delicate tooth extraction and curettage with or without the elevation of full-thickness flaps + PRF directly over the bone to fill the socket + 4.0 nylon sutures	PRF Amoxicillin 250 mg every 8 h for 1 week starting from the morning of the surgery (in case of allergy to penicillin, clindamycin was administered at a dosage of 150 mg every 6 h for 1 week) CTR	1,2,4,8,12 w	PRF 12 w: 100% positive CTR 4 w: 9 patients (12 ex) delayed recovery with bone exposure 12 w: 100% positive

(*continued on next page*)

Table 4 (*continued*)

Reference	Number of sites treated	Sites Mand/Max	Procedure	Type of surgical intervention	Antibiotics	Follow-up	Outcome
					As a historical CTR, only 28 of the 73 patients in the CTR group were prophylactically treated with various antibiotics such as amoxicillin, cefcapene, or clindamycin for several days.		
Vlad et al. (2017)	37	–	Tooth extraction	After the dental extracts, the alveolar bone was covered with the A-PRF membranes over which the gingival mucous membrane was sutured.	Post-operative (not specified)	7–30 days	7 d: 14,3% dehiscence 30 d: 100% healed

CTR: Control.

the information concerning tubes, speed, and centrifugation time (Miron et al., 2019).

Growth factors released by platelets include platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β), insulin-like growth factor-1 (IGF-I), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) (Etulain 2018). These growth factors have been shown to be chemotactic for various cell types, creating tissue micro-environments and directly influencing the proliferation and differentiation of progenitor cells (Miron et al., 2017).

In an animal study on a rat model of bisphosphonate-related osteonecrosis of the jaw, PDGF exhibited therapeutic effects by enhancing angiogenesis and osteogenesis (Gao et al., 2019).

The different release of growth factors seems to be related to the polymerization modalities of the APCs: PRP and PRGF polymerization is chemically induced with a sudden reaction that leads to an uncontrolled and short-term release of growth factors; PRF polymerizes naturally and slowly during centrifugation, which produces a slow release of growth factors that seems to persist for at least 14 days (He et al., 2009).

Furthermore, APCs act as a membrane in avoiding direct contact between bone and oral mucosa which could be useful in preventing direct toxicity on the soft tissues of bisphosphonates released from bone after surgery (Choukroun et al., 2006; Nørholt and Hartlev 2016).

Table 5
Assessing the Quality of Reports of Clinical Trials of MRONJ prevention with Jadad scale.

	ITEMS	
	Mozzati et al. (2012b)	Asaka et al. (2016)
Was the study described as randomized?	Yes	No
Was the study described as double-blind?	No	No
Was there a description of withdrawals and dropouts?	No	Yes
Was the method for generating the randomization sequence described and appropriate?	No	No
Was the double-blind method described and appropriate?	No	No
SCORE	1	1

4.1. MRONJ prevention

The results of this review highlighted similar results in terms of MRONJ incidence with or without the use of APC after oral surgery procedures in patients with a history of antiresorptive treatment.

Statistical analysis showed no difference between the two groups (APCs vs. no APCs) in the prevention of MRONJ after dental extractions.

Out of a total of 1219 dental extractions recorded, only 12 cases of MRONJ have been reported (1%), all in patients with a history of high-dose antiresorptive treatment and regardless of the use of APCs (Scoletta et al., 2011; Mozzati et al., 2012b; Scoletta et al., 2013).

Asaka et al. reported a delayed recovery with bone exposure after four weeks for nine patients (12 extractions) with complete healing after 12 weeks, considering a retrospective control group of 73 patients (166 extractions); all patients treated with PRF showed complete healing after four weeks (Asaka et al., 2016).

Regarding the use of APCs as a preventive measure in implant surgery, no cases of MRONJ were reported in a long follow-up (up to 9 years) in 237 patients (1277 implants placed, 56 procedures of sinus augmentation). All patients received low-dose antiresorptive therapy (Torres et al., 2008; Mozzati et al., 2015; Cucchi et al., 2016).

An uncritical analysis of the results would suggest a lack of benefits in the use of APCs as an additional preventive measure after oral surgery procedures in patients treated with antiresorptive drugs.

On the other hand, recent *in vitro* and animal model studies seem to emphasize a possible role of APCs in the prevention of MRONJ after oral surgery procedures (Steller et al., 2019; Toro et al., 2019).

There are main biases in the articles examined in the review, concerning the type of study, the characteristics of the patients included (time, type and route of administration of the drugs, comorbidity and habits), and the dissimilar medical and surgical protocols used (different APCs used, flap or flapless surgery, antibiotic therapy).

Table 6
Data of MRONJ prevention studies regarding dental extractions analyzed with the Fisher's exact test.

	Complete healing	MRONJ
APCs after dental extractions	779	7
No APCs after dental extractions	428	5

$p = 0.7634$.
The result is not significant at $p < .05$.

Table 7
General features of the studies on MRONJ treatment.

	Reference	Number of patients	Mean age (range), years	Gender M/F	Primary cause of disease	Drugs administered	Time of drug treatment (average or other specified)	Comorbidities, other habits/medications
PRP	Adornato et al. (2007)	12	63.9 (43–83)	4/8	Breast cancer 8 MM 3 Prostatic cancer 1	HD Z 8 P 4	At least 1 y	Smoking 2
	Antonini et al. (2010)	1	72	0/1	Breast cancer	HD Z	4 y	-
	Bernardi et al. (2018)	1	68	0/1	Osteoporosis	LD I	-	-
	Bocanegra-Perez et al. (2012)	8	66.25	2/6	Breast cancer 2 MM 4 Osteoporosis 2	HD Z 3 Z + P 2 Z + P + C 1 LD A 2	-	Corticosteroids 5 Non-insulin-dependent diabetes mellitus 6
	Cetiner et al. (2009)	Total: 5 Conservative: 3 Surgery: 1 Surgery + PRP: 1	Total: 60.8 (52–68) Conservative: 59.3 (52–68) Surgery: 58 Surgery + PRP: 68	Total: 4/1 Conservative:2/1 Surgery: 1/0 Surgery + PRP: 1/0	MM	HD Z	25.16 ± 17.4 m (range 5–76 m)	Thalidomide/ dexomethasone 4
	Coviello et al. (2012)	Total: 7 Surgery: 4 Surgery + PRP: 3	Total: 75.57 (66–84) Surgery: 75.25 (66–80) Surgery + PRP: 76 (69–84)	Total: 2/5 Surgery: 1/3 Surgery + PRP: 1/2	MM	HD Total: Z 4 Z + P 3 Surgery: Z 1 3 Z + P Surgery + PRP: 3 Z	8.5 y Z 2.45 y Z + P	-
	Curi et al. (2007)	3	66.3	0/3	Breast cancer 2 MM 1	HD Z	8.5 y	-
	Curi et al. (2011)	25	60,7	5/20	Breast cancer 14 Prostate cancer 4 MM 7	HD Z 21 P 4	2.3 y (range 1–7 y)	Chemotherapy 24 Corticosteroids 7
	Lee et al. (2007)	2	80 (76–84)	1/1	Osteoporosis	LD A	5-9 y	Hypertension, chronic pulmonary obstructive disease (COPD), pneumonia
	Longo et al. (2014)	Total: 72 (conservative non-surgical therapy, patients without improvement underwent surgery and were divided into the following two groups) Surgery: 15 Surgery + PRP: 34	59 (37–81)	12/60	Breast cancer 54 Lung cancer 8 MM 1 Prostatic cancer 9	HD A 2 P 22 Z 48	4–62 m	-
	Martins et al. (2012)	Total: 22 Conservative: 3 Surgery: 5 Surgery + PRP: 14	Total: 58.09 (42–90) Conservative: 67.3 (60–71) Surgery: 59.4 (50–74) Surgery + PRP: 55.64 (42–90)	Total: 6/16 Conservative: 0/3 Surgery: 1/4 Surgery + PRP: 5/9	Total: Breast cancer 14 (59%) Lung cancer 1 (5%) MM 1 (9%) Prostatic cancer 6 (28%) Conservative: Breast cancer 3 Surgery: Breast cancer 4 MM 1 Surgery + PRP:	HD Total: P 4 Z 18 Conservative: Z 3 Surgery: Z5 Surgery + PRP: Z 10 P 4	Total: 24.68 m (range 8–48 m) Conservative: 27.3 m (range 24–48 m) Surgery: 22.6 m (range 18–30 m) Surgery + PRP: 22.57 m (range 8–48 m)	Chemotherapy 21 Corticosteroids 13 4 Diabetes 4

(*continued on next page*)

Table 7 (*continued*)

	Reference	Number of patients	Mean age (range), years	Gender M/F	Primary cause of disease	Drugs administered	Time of drug treatment (average or other specified)	Comorbidities, other habits/medications
					Breast cancer 7 Lung cancer 1 MM 1 Prostatic cancer 5			
	Mathias et al. (2013)	Total: 13 Conservative: 3 Surgery: 4 Surgery + PRP: 6	Total: 67.3 (48–84) Conservative: 67 (55–82) Surgery: 66 (48–74) Surgery + PRP: 68.33 (54–84)	Total: 12/1 92.3% M 7.7% F Conservative: 0/3 Surgery: 0/4 Surgery + PRP: 1/5	Total: Breast cancer 9 Osteoporosis 3 Prostatic cancer 1 Conservative: Breast cancer 1 Osteoporosis 2 Surgery: Breast cancer 4 Surgery + PRP: Breast cancer 4 Osteoporosis 1 Prostatic cancer 1	Total: HD Z 7 P 2 Z + P 1 LD A 3 Conservative: HD Z 1 LD A 2 Surgery: HD Z 2 P 2 Surgery + PRP: HD Z 5 LD A 1	-	Cardiovascular disease 1 Diabetes and hypertension 1
	Mauceri et al. (2018)	10	75.2 ± 5.94	3/7	Breast cancer 3 MM 4 Prostate cancer 3	HD Z 9 Z + I 1	31,8 ± 25,76 m	Chemotherapy 5 Corticosteroids 2 Diabetes 2 Hypertensions 6 Osteoporosis 5 Rheumatoid arthritis 1 Smokers 2
	Merigo et al. (2018)	21	72.6 (60–85)	5/16	Breast cancer 7 Kidney cancer 1 Pancreas cancer 1 Prostate cancer 2 Osteoporosis + Reumatoid Arthritis 1 Osteoporosis 8 Reumatoid arthritis 1	HD Z 8 Z + S 3 LD A 10	5–164 m	Arhythmia – Gastritis 1 Corticosteroids 6 Diabetes 1 Hypertensions 6 Venous thrombosis 1 Smokers 3
	Vairaktaris et al. (2009)	1	72	0/1	Breast cancer	HD P	3 y	Prothrombin gene G21020A mutation (associated with thrombophilia)
PRGF	Anitua et al. (2013)	1	50	0/1	Cancer	HD Z	3 y	-
	Garcia-Gil et al. (2019)	1	65	0/1	Osteoporosis	LD A	1 y	Epilepsy Hypertension
	López et al. (2019)	3	69.3 (61–80)	0/3	Breast cancer 1 Osteoporosis 2	HD Z 1 LD R 1 I 1	Case 1 9 y Case 2 6 y Case 3 3 y	Smoking 1 Radiotherapy, and Chemotherapy 1

	Mozzati et al. (2012a)	32	69.7 (44–83)	10/22	Breast cancer 5 Lung carcinoma 4 MM 14 Ovarian carcinoma 3 Prostatic carcinoma 6	HD Z 26 P 6	37 m	Chemotherapy 4 Corticosteroids 11 Smoking 12
PRF	Bilimoria et al. (2017)	5	65.6 (46–82)	2/3	Breast cancer 1 MM 3 Osteoporosis 1	HD Z 3 Z + D 1 LD BP + Z	HD 5.75 y (range 2–10 y) LD 11 y	Lupus, Sickle-cell anaemia 1
	De Castro et al. (2016)	2	48.5 (46–51)	0/2	Osteoporosis	LD A	Case 1 6 y Case 2 n.s.	Corticosteroids 1 Diabetes 1 Systemic lupus erythematosus 1
	Dinca et al. (2014)	10	59 ± 15 (30–79)	4/6	Bowel cancer 1 Breast cancer 3 Kidney cancer 1 Prostatic cancer 3 MM 2	HD Z 7 I 3	-	-
	Giudice et al., 2018a, 2018b	Total: 47 Surgery: 23 Surgery + PRF: 24	Total: 74.7 ± 6.5 (58–83) Surgery: 73.9 ± 7.4 (62–83) Surgery + PRF: 75.5 ± 5.6 (58–83)	Total: 24/23 Surgery: 14/9 Surgery + PRF: 14/10	Total: Breast cancer 11 Kidney cancer 5 Lung cancer 3 MM 1 Osteoporosis 12 Prostatic cancer 15 Surgery: Breast cancer 5 Kidney cancer 2 Lung cancer 2 MM 1 Osteoporosis 7 Prostatic cancer 5 Surgery + PRF: Breast cancer 6 Kidney cancer 3 Lung cancer 1 Osteoporosis 5 Prostatic cancer 10	Total: HD D 9 Z 26 LD A 10 D 1 I 1 Surgery: HD Z 12 D 4 LD A 5 D 1 I 1 Surgery + PRF: HD Z 14 D 5 LD A 5	-	-
	Gönen and Yılmaz Asan (2016)	1	77	1/0	Prostatic cancer	HD Z	2 y	Coronary disease
	Inchingolo et al. (2017)	23	- (52–73)	8/15	-	-	-	-
	Kim et al. (2014)	34	71 ± 13	0/34	Bone metastasis 2 Osteoporosis 32	HD Z 3 LD A 19 R 8 P 4	78 m (range 21–92 m)	Chemotherapy 2 Diabetes 7 Obesity 4 Taking steroids 4 Renal failure 1
	Maluf et al. (2016)	2	Case 1, 69 Case 2, 44	1/1	Breast cancer 1 Lung cancer 1	HD D 1 B + D 1	Case 1, 8 m Case 2, 7 m	-
	Maluf et al. (2018)	2	Case 1, 79 Case 2, 75	0/2	Breast cancer 2	HD Z	-	Allergy to penicillin 1 Sjögren's syndrome 1
	Mourão et al. (2019)	11	67.7 ± 14.6 (38–84)	2/9	Osteoporosis	LD A	57.6 ± 14.7 m (range 36–84 m)	-

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Table 7 (*continued*)

Reference	Number of patients	Mean age (range), years	Gender M/F	Primary cause of disease	Drugs administered	Time of drug treatment (average or other specified)	Comorbidities, other habits/medications
Nørholt and Hartlev (2016)	15	68.5 (54–83)	4/11	Breast cancer 4 Kidney cancer 2 MM 1 Osteoporosis 7 Prostatic cancer 1	HD D 2 I 1 P 1 Z 4 LD A 5 D 2	HD:34 m (range 15 −73 m LD: 126 m (range 48 −240 m)	-
Saad D and Saad P (2017)	1	64	0/1	Osteoporosis	LD I + D	I 1 y D 2 y	-
Sahin et al. (2019)	1	63	0/1	Osteoporosis	LD D	7 y	Hypertension 1
Soydan and Uckan (2014)	1	75	1/1	MM	HD Z + P	3 y	Diabetes Prostate enlargement
Tsai et al. (2016)	1	79	0/1	Osteoporosis	LD Z + A	A 10 y Z 1 y	-
Valente et al. (2019)	14	64 (56–71)	6/9	Breast cancer 2 Melanoma 1 MM 1 Osteoporosis 8 Prostatic cancer 3	HD D 2 I 1 Z 5 LD A 3 D 2 I 2	2-6 y	Arthritis 1 Atrial fibrillation 3 Cardiovascular disease 13 Diabetes 4 Gastritis 4 Hypercholesterolemia 5 Hypertension 12 IMA 2 IRC 1 M. Parkinson 1 Smoking 1

Z: zoledronic acid.
P: pamidronic acid.
I: ibandronic acid.
C: clodronic acid.
R: risedronic acid.
S: sunitinib.
B: bevacizumab.
A: alendronic acid.
HD: high-dose drug treatment.
LD: low-dose drug treatment.
CR: case reported.
n.s.: not specified.
BP: bisphosphonate not specified.
MM: multiple myeloma.

Table 8
Specific features and outcomes of the studies on MRONJ treatment.

	Reference	Number of lesions	Site	Staging AAOMS (specified if different)	Type of surgical intervention	Antibiotics	Follow-up	Outcome
PRP	Adornato et al. (2007)	12	Mandible 8 Maxilla 4	-	Bone resection + PRP	Clindamycin 300 mg x 4/d for 10 d	6 m	Complete response 10 Negative response 2
	Antonini et al. (2010)	1	Maxilla	Stage 3	Bone resection + HBO + PRP	Cephalexin 500 mg x 4/d for 10 d	12 m	Complete response
	Bernardi et al. (2018)	1	Mandible	Stage 3	Debridement and fracture reduction (GA) + PRP	-	12 m	Complete response
	Bocanegra-Perez et al. (2012)	10	Mandible 9 Maxilla 1	Stage 2	Bone resection + PRP	-	Average 14 m (range 12–26 m)	Complete response
	Cetiner et al. (2009)	Total: 8 Conservative: 6 Surgery: 1 Surgery + PRP: 1	Total: Mandible 5 Maxilla 3 Conservative: Mandible 3 Maxilla 3 Surgery: Mandible 1 Surgery + PRP: Mandible 1	Stage 2–3	Conservative non-surgical treatment Minor surgical debridement Bone resection + PRP	Amox/clav 1 g x 2/d or Clindamycin 150–300 mg x 2–4/d	6 m	Conservative Complete response - Partial response 5 Negative response 1 Surgery Complete response - Partial response - Negative response 1 Surgery + PRP Complete response 1 Partial response - Negative response -
	Coviello et al. (2012)	Total: 9 Surgery: 5 Surgery + PRP: 4	Total: Mandible 7 Maxilla 2 Surgery: Mandible 4 Maxilla 1 Surgery + PRP: Mandible 3 Maxilla 1	-	Debridement + sequestrectomy Debridement + sequestrectomy + PRP	Amox/clav 1 g x 2/d for 14 d	3 m	Surgery Complete response - Partial response 2 Negative response 3 Surgery + PRP Complete response 4 Partial response - Negative response -
	Curi et al. (2007)	3	Mandible 3	-	Bone resection + PRP	Clindamycin 300 mg x 4/d for 14 days	6 m	Complete response 2 Partial response 1
	Curi et al. (2011)	25	Mandible 18 Maxilla 7	Stage 1 3 Stage 2 15 Stage 3 7	Partial bone resection (GA) + PRP	Clindamycin 600 mg i.v. for 7 days	36 m	Complete response 20 Negative response 5

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Table 8 (*continued*)

Reference	Number of lesions	Site	Staging AAOMS (specified if different)	Type of surgical intervention	Antibiotics	Follow-up	Outcome
Lee et al. (2007)	2	Mandible 1 Maxilla 1	-	Surgical debridement + PRP Case 1: HBO	Penicillin i.v. for 3 m, then oral penicillin VK for 3 m	7 m	Complete response
Longo et al. (2014)	Total: 72 (conservative non-surgical therapy, lesions without improvement underwent surgery and were divided into the following two groups) Surgery: 15 Surgery + PRP: 34	-	Total: Stage 0 5 Stage 1 11 Stage 2 41 Stage 3 15 Surgery: Stage 1 2 Stage 2 7 Stage 3 6 Surgery + PRP: Stage 1 1 Stage 2 26 Stage 3 7	Surgical debridement Surgical debridement + PRP	Phenoxymethylpenicillin, amoxicillin, amox/clav, or clindamycin with or without metronidazole	6–94 m	Surgery Complete response 8 Partial response 7 Surgery + PRP Complete response 32 Partial response 2
Martins et al. (2012)	Total: 24 Conservative: 3 Surgery: 5 Surgery + PRP: 16	Total: Mandible 19 Maxilla 5 Conservative: Mandible 2 Maxilla 1 Surgery: Mandible 5 Surgery + PRP: Mandible 12 Maxilla 4	Total: Stage 1 9 Stage 2 10 Stage 3 7 Conservative: Stage 1 3 Surgery: Stage 1 4 Stage 2 1 Surgery + PRP: Stage 1 2 Stage 2 9 Stage 3 3	Antibiotic therapy and irrigation with antiseptic (chlorhexidine 0.12%) Sequestrectomy and/or ostectomy and/or osteoplasty Sequestrectomy and/or ostectomy and/or osteoplasty + PRP + laser phototherapy (LPT)	Clindamycin 300 mg or amoxicillin 500 mg for a minimum of 7 days	6 m	Conservative Complete response 1 Partial response 2 Surgery Complete response 3 Partial response 2 Surgery + PRP Complete response 15 Partial response 1
Mathias Duarte et al. (2013)	Total: 14 Conservative: 3 Surgery: 4 Surgery + PRP: 7	Total: Mandible 9 Maxilla 5 Conservative: Mandible 3 Surgery: Mandible 1 Maxilla 3 Surgery + PRP: Mandible 5 Maxilla 2	Stage 2	Antibiotic therapy and irrigation with antiseptic (chlorhexidine 0.12%) Surgical resection Surgical resection + PRP	Clindamycin 300 mg every 6 h	-	Conservative Complete response 2 Partial response - Negative response 1 Surgery Complete response - Partial response

								3 Negative response 1
								Surgery + PRP Complete response 3 Partial response 3 Negative response 1
	Mauceri et al. (2018)	10	Mandible 9 Maxilla 1	SICMF-SIPMO staging Stage 1 B, 6 Stage 2 A, 2 Stage 2 B, 2	Surgical debridement and sequestrectomy (if required) with Er,Cr:YSGG laser + PRP	Ampicillin/sulbactam 1 g (i.m.) x 2/d + Metronidazole: 500 mg (per os) x 3/d starting 1 d before surgery and for 7 d	15 d 1,3,6,12 m	Complete response 3 Partial response 5 Negative response 2
	Merigo et al. (2018)	21	Mandible 6 Maxilla 15	Stage 1 2 Stage 2 15 Stage 3 4	Piezosurgery Er:YAG laser device + PRP	Amox/clav 2 g/d and metronidazole 500 mg/d per os (or clindamycin in case of allergy), starting 3 d before surgery and for at least 2 w	9.6 months	Complete response 20 Partial response 1
	Vairaktaris et al. (2009)	1	Mandible	-	Bone resection + PRP	-	4 m	Partial response
PRGF	Anitua et al. (2013)	1	Mandible	-	Bone resection + PRGF	-	12 m	Complete response
	Garcia-Gil et al. (2019)	1	Mandible	-	Surgical osteotomy + PRGF	Amox/clav 875/125 mg for 7 d	3,6,12,24 m	Complete response
	Lopez et al. (2019)	3	Mandible	Stage 2	Bone resection + PRGF	Amoxicillin 2 g 1 h before surgery Amoxicillin 500 mg x 3/d for 10 d in Cases 2 and 3, for 21 d in Case 1	30 m	Complete response
	Mozzati et al. (2012a)	32	Mandible 24 Maxilla 8	Stage 2 B	Marginal resection surgery with Piezosurgery + PRGF	Amoxicillin 1 g x 2/d from 1 d before the surgery and for 5 d after	48–50 m	Complete response
PRF	Bilimoria et al. (2017)	6	Mandible 4 Maxilla 2	Stage 2	Piezoelectric surgery + L-PRF	Amoxicillin 500 mg + metronidazole 400 mg x 3/d for 7 d	12 m	Complete response 5 Partial response 1
	De Castro et al. (2016)	2	Mandible 2	Stage 2 1 Stage 3 1	Surgical debridement + photodynamic therapy (PDT) + PRF	Case 1 Amox/clav 1 g + Metronidazole 400 mg x 3/d for 15 d Case 2 Clindamycin 300 mg x 3/d for 7 d	Case 1 10 m Case 2 14 m	Complete response
	Dinca et al. (2014)	10	Mandible 7 Maxilla 3	Stage 2	Sequestrectomy + bone curettage + PRF	Amox/clav 1 g x 4/d for 10 d	30 d	Complete response
	Giudice et al., 2018a, 2018b	Total: 61 Surgery: 28 Surgery + PRF: 33	Total: Mandible 49 Maxilla 12 Surgery: Mandible 22 Maxilla 6 Surgery + PRF: Mandible 27 Maxilla 6	Total: Stage 2 27 Stage 3 20 Surgery: Stage 2 13 Stage 3 10	Bone curettage Bone curettage + PRF	Amoxicillin 1 g x 2/d + metronidazole 250 mg x 3/d or clindamycin 600 mg x3/d start 3 d before surgery, for 10 d	T1: 1 m T2: 6 m T3: 12m	Surgery Complete response 26 Negative response 2 Surgery + PRF Complete response 32 Negative response 1

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Table 8 (*continued*)

Reference	Number of lesions	Site	Staging AAOMS (specified if different)	Type of surgical intervention	Antibiotics	Follow-up	Outcome
			Surgery + PRF: Stage 2 14 Stage 3 20				
Gönen and Yılmaz Asan (2016)	1	Mandible	Stage 3	Curettage + Sequestrectomy + PRF	Amox/clav 1 g + metronidazole 500 mg	18 m	Complete response
Inchingolo et al. (2017)	23	-	-	Sequestrectomy with Piezosurgery + PRF	Amox/Clav 1 g x 2/d start 1 h before surgery, for 8 d	30 d	Complete response
Kim et al. (2014)	34	Mandible 27 Maxilla 7	Stage 1 7 Stage 2 21 Stage 3 6	Curettage + Sequestrectomy + PRF	Third generation cephalosporin i.v. 1 g x 2/d	1, 4 m	Complete response 26 Partial response 6 Negative response 2
Maluf et al. (2016)	2	Mandible 2	Stage 2	Bone resection and osteotomy with a rotary instrument + PRF	Penicillin/Clavulanate 875 mg	Case 1 4 m Case 2 6 m	Partial response
Maluf et al. (2018)	2	Mandible 1 Maxilla 1	Stage 2 Stage 3	Surgical debridement + L-PRF	Case 1 Amox/clav 1 g + metronidazole 250 mg for 1 w Case 2 Ciprofloxacin 500 mg for 4 w	Case 1 52 m Case 29 m	Complete response
Mourão et al. (2019)	11	Mandible 7 Maxilla 4	Stage 2	Surgical debridement + PRF	Amox/clav 1 g x2/d for 9 d (start 1 d before)	23.5 ± 8.7 m (range 12–36 m)	Complete response
Nørholt and Hartlev (2016)	17	Mandible 13 Maxilla 4	Stage 2 13 Stage 3 4	Bone resection + PRF	Penicillin 2 MIU + metronidazole 1 g preoperatively Penicillin 1 MIU x 4/d for 4 w Metronidazole 500 mg x 2/d for 5 d Clindamycin 600 mg x 3/d in case of allergy to penicillin	12 m (range 7–20 m)	Complete response 15 Negative response 2
Saad D and Saad P (2017)	1	Maxilla	Stage 2	Osteotomy with Piezosurgery + PRF	Amoxicillin/Clavulanic Acid for 7 d	12 m	Complete response
Sahin et al. (2019)	1	Maxilla	-	Surgical treatment with piezo + L-PRF + BFP	Amox/clav 1 g + Metronidazole 500 mg	1,3,6,12 m	Complete response
Soydan et Uckan (2014)	1	Maxilla	-	Bone curettage + PRF	Amox/clav 1 g + Metronidazole 500 mg for 3 w	6 m	Complete response
Tsai et al. (2016)	1	Mandible	Stage 3	Saucerization and sequestrectomy + PRF (GA)	Ciprofloxacin 750 mg/d for 3 m	10 m	Complete response
Valente et al. (2019)	14	Mandible 8 Maxilla 6	Stage 0 1 Stage 1 4 Stage 2 9 Stage 3 1	Surgery + PRF 14	Amoxicillin 2–3 g/d Clindamycin 900–1200 mg/d Ciprofloxacin 500 mg/d for 3–9 w	42.2 m (range 6–74 m)	Complete response 10 Negative response 4

HBO: hyperbaric oxygen therapy.
Amox/clav: amoxicillin + clavulanate.
GA: under general anesthesia.
i.v.: intravenous administration.
i.m.: intramuscular administration.
BFP: Buccal fat pad.

Table 9
Assessing the Quality of Reports of Clinical Trials of MRONJ treatment with Jadad scale.

	ITEMS	
	Coviello et al. (2012)	Giudice et al., 2018a,2018b
Was the study described as randomized?	Yes	Yes
Was the study described as double-blind?	No	No
Was there a description of withdrawals and dropouts?	No	Yes
Was the method for generating the randomization sequence described and appropriate?	No	Yes
Was the double-blind method described and appropriate?	No	No
SCORE	1	3

Table 10
Data of MRONJ Treatment studies analyzed with the Fisher's exact test.

	Improvement (complete or partial response)	No response
APCs after surgery	325	19
Surgery alone	51	17

$p = 0.0788$.
The result is not significant at $p < .05$.

4.2. MRONJ treatment

The results of this review showed better rates of healing of MRONJ lesions with application of APCs in addition to surgical treatment (87.8% vs. 63.8%), but the main bias concerns the unspecified definition of "healing" in almost all the articles examined.

The outcome of a treatment can be defined as successful when there is an improvement of a disease (transition from a severe to a milder state) or when there is a definitive resolution. Interpreting the results of studies concerning the treatment of MRONJ is complicated, even for the numerous clinical variables that affect treatment response (Lopez-Jornet et al., 2016).

The application of APCs after surgical treatment showed complete response in 302 lesions (87.8%), partial response in 23 lesions (6.7%), and negative response in 19 lesions (5.5%); surgical treatment alone showed complete response in 37 lesions (63.8%), partial response in 14 lesions (24.1%), and negative response in seven lesions (12.1%).

Statistical analysis showed no difference between the two groups (APCs vs. no APCs) in the surgical treatment of MRONJ in terms of the patient's disease improvement.

Many authors have reported promising results in terms of absence of bone exposure after applying APCs postoperatively. Unfortunately, in some cases the use of APCs is associated with other therapies confounding the outcome of the treatment.

In the only randomized clinical trial included in this review, Giudice et al. studied the effect of applying PRF on bone after surgical debridement of MRONJ lesions. At various follow-up visits, in terms of mucosal healing and quality of life, comparing the results to traditional bone surgery: a long-term evaluation showed no statistical differences between the PRF and non-PRF groups in terms of mucosal healing and absence of infection, but the short-term follow-up showed significant improvement in terms of quality of life in favor of the PRF group (Giudice et al., 2018b).

As for MRONJ prevention studies, there are main biases in the articles examined concerning the type of study, the characteristics of the patients included, and the dissimilar medical and surgical protocols used (different APCs used; conventional, piezoelectric, or laser surgery; antibiotic therapy).

5. Conclusion

The application of APCs may be helpful in the treatment and prevention of MRONJ because of their local immunomodulatory properties and possible promotion of angiogenesis and tissue healing by platelet factors, but considering the limitations of this systematic review (**no studies eligible for meta-analysis**, very few randomized studies, no multicentric studies, lack of or different definition of treatment success, small samples, heterogeneous drug administrations, different protocols, and so on), our results are not sufficient to prove its effectiveness.

Further randomized controlled studies are needed to establish whether the use of APCs could, on the one hand, significantly reduce the incidence of MRONJ after oral surgery procedures in patients treated with antiresorptive drugs and, on the other, improve healing and quality of life in patients with MRONJ requiring surgical treatment.

Declaration of Competing Interest

The authors declare that they have no competing interests related to this study. No financial support was received.

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