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Autologous platelet concentrates in treatment of medication related osteonecrosis of the jaw

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SUMMARY

Background. Medication related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction occurring as a progressive bone destruction in the maxillofacial region. MRONJ is usually initiated after oral surgery procedures, however periodontal disease and other chronic inflammations are also risk factors. There is no clear treatment protocol for management of MRONJ, for this reason autologous platelet concentrates (APC) have been introduced to enhance the healing process.

Aim. To evaluate the effectiveness of APCs in treatment of MRONJ.

Methods. A systematic literature review was performed according to PRISMA guidelines in MEDLINE (PubMed) and Google Scholar databases. Only no older than 5 years, in vivo studies in English with follow-up until condition totally resolves were included.

Results. A total of 2683 publications were identified out of which only 7 met the inclusion criteria, 6 cohort and 1 randomized clinical trial. Most of the studies preferred platelet rich fibrin (PRF) and only one used platelet rich plasma (PRP) in MRONJ treatment. MRONJ stage, patients mean age, drug therapy, follow-up and success rate were analysed in all the studies. Five studies also named how MRONJ initiated and 4 studies mentioned duration of drug intake before developing MRONJ.

Conclusion. The published data is not sufficient to confirm a specific treatment protocol although the published results are promising. More prospective randomized controlled clinical trials are required in order to evaluate the effectiveness of APCs for treatment of MRONJ.

Key words: osteonecrosis, medication, platelet, concentrates, surgery.

INTRODUCTION

Medication related osteonecrosis of the jaw (MRONJ) is a progressive bone destruction in the maxillofacial region caused by either antiresorptive (bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors) or antiangiogenic drugs. Although MRONJ was first described by Marx in 2003 (1), to this day the pathophysiology is not clearly defined. There are several hypotheses that might explain the localization of osteonecrosis: inflammation, infection, altered bone remodelling, inhibition of angiogenesis, suppression of immunity or over suppression of bone resorption. Due to the unknown MRONJ pathogenesis dental, maxillofacial procedures for the patients taking one of the mentioned drugs are either postponed or carried out before prescribing treatment (2).

MRONJ usually develops after oral surgery procedures, such as tooth extraction, implantation or periodontal curettage. Periodontal disease (PD) and other chronic inflammations were previously described as risk factors for development of osteonecrosis. MRONJ is diagnosed by observation of exposed bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws (3). Osteonecrosis treatment depends on the stage (Table 1): ranging from symptomatic treatment, conservative management of caries and periodontal disease, antibiotics, antimicrobial rinses to surgical debridement of wound, sequestrectomy and resection. Usually Stage

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2&3 requires surgical approach in combination with antibiotic therapy and antimicrobial rinses (4).

As the lower MRONJ stages are not difficult to treat, the choice between conservative and surgical approach is not easy – treatment tactic should be decided by a multidisciplinary team, including maxillofacial surgeon, oncologist and dentist for each case of stage 2 or 3. It is advised to manage the disease as conservative as possible, since the surgical management is not always successful and creates a new surgical site in avascular region. Reduced angiogenesis in MRONJ site compromises access of monocytes/macrophages and infection-fighting cytokines in the affected area (5).

The average healing duration to achieve a complete remission takes a long time, ranging from 7 to 19 months (6), conservative treatment seems to be successful only in 50% of cases (7-9), while surgical treatment success rate ranges from 23% to 100%. The relatively low success rate of MRONJ relies on the extension of marginal bone resection, which is difficult to determine – it is based on clinical findings during surgery: bone colour, bleeding (as a sign of vitality) and the procedure itself is not easily performed – it requires an experienced maxillofacial surgeon (10).

Autologous platelet concentrates (APC) like platelet rich fibrin (PRF) or plasma rich in growth factors (PRGF) come to use in treating MRONJ as the mentioned products have specific growth factors, which induces a crucial element in wound healing – angiogenesis (11). These factors include platelet-derived growth factors (PDGF), transforming growth factor β1 (TGF-β1), vascular endothelial growth factor (VEGF), similar to insulin growth factor-1 (IGF-I) and others. APC enhances healing by bringing leukocytes, stimulating collagen formation, producing anti-inflammatory agents and initiating vascular internal growth. Platelet concentrates are used widely in medicine and have a strong biological justification (12), meaning APC could be used in addition to surgical debridement during treatment of MRONJ.

METHODS

A systematic literature search was performed according to PRISMA guidelines in search of clinical trials published between 2014 and 2020, since the search started in December, 2019. Electronic and manual literature searches were conducted independently by all authors in several databases, including MEDLINE (PubMed) and Google Scholar. The titles and abstracts first were analysed, followed by the selection of complete articles for careful reviewing and analysis according to the eligibility criteria.

Selected studies were published in English and no older than 5 years, describing in vivo studies evaluating the use of autologous platelet concentrates in treatment of MRONJ with follow-up until condition totally resolves. All case reports, animal and in vitro studies were excluded.

The quality of selected cohort studies was assessed using the Newcastle-Ottawa scale, where the total maximum score is 9. Studies which scored ≥7 were considered as a high-quality (Table 2). Cochrane Risk of Bias Tool was used for randomized clinical trial (RCT) quality evaluation (Table 3).

Keywords: osteonecrosis, medication, platelet, concentrates, surgery.

RESULTS

The combinations of search terms identified a total of 2683 titles. After removal of duplicates, 2023 records remained. Of these, 2013 did not meet the inclusion criteria (editorial, comments, experimental, case reports, animal studies, publication date <5 years), leaving 10 manuscripts for more detailed review. Finally, 7 manuscripts fulfilled all inclusion criteria and underwent systematic review (Figure, Table 4).

The included manuscripts were mostly Cohort studies, only 1 randomised control trial met the re-

Table 1. Staging of Medication Related Osteonecrosis of the Jaw

Stage	Symptoms
At risk	No apparent exposed/necrotic bone in patients who have been treated with either antiresorptive or antiangiogenic agents
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage 1	Exposed, necrotic bone or fistula that probes to bone No symptoms or evidence of infection
Stage 2	Exposed, necrotic bone or fistula that probes to bone, associated with infection, pain, and erythema in the regions of the exposed bone Purulent drainage may also be present
Stage 3	Exposed, necrotic bone or fistula that probes to bone in patients with pain, infection, and 1 or more of the following: pathologic fracture, extraoral fistula, oral antral/oral nasal communication or osteolysis extending to the inferior border or sinus floor

quirements for inclusion, the heterogeneity of studies limited the ability to perform data meta-analysis.

Autologous platelet concentrates: types

Three APCs were mostly described and used in literature – platelet rich fibrin (6), platelet rich plasma (PRP) (1) and plasma rich in growth factors, only articles with use of PRP and PRF met the requirements and were included in analysis. Platelet rich fibrin (PRF) seems to be the most favourable APC probably due to the slow release of growth factors (7-28 days).

Drug therapy

Participants were being treated by one of the bisphosphonates: alendronate, zoledronate, ibandronate, pamidronate or risedronate. Denosumab was also used in 18 cases. Zoledronate was used the most frequently (54 cases). Four out of seven studies mentioned duration of treatment before developing MRONJ.

Patient's data

The mean age among patients in reviewed articles ranged from 59 to 75.2 years. A total of 142 patients participated in 7 trials. Second stage of MRONJ was the most frequent among them (95 cases). Five out of seven studies mentioned how MRONJ initiated, extraction (50 cases) being the most frequent reason.

Treatment outcomes

The success rate in reviewed articles ranged from 73.3% to 100%. The measurements were made by clinical examination (no signs of infection, mucosal integrity) and radiographical examination (panoramic x-ray).

In the randomised control trial of Giudice et al. (19), 47 patients with stage II and III of MRONJ were randomly assigned to control group (surgical necrotic bone removal) and experimental group (surgical removal and PRF). Patients were evaluated at 1 month (T1), 6 months (T2), and 1 year (T3) after treatment. Clinical postoperative conditions were evaluated by analysing the following outcomes:

Table 2. Application protocol for universal adhesive

Study	Selection				Comparability of cohorts on the basis of the design or analysis (**)	Outcomes			Total score (out of 9)
	Representativeness of the exposed cohort (*)	Selection of the non-exposed cohort (*)	Ascertainment of exposure (*)	Outcome not present at the start of the study (*)		Assessment of outcome (*)	Length of follow-up (*)	Adequacy of follow-up (*)	
Norholt SE. *et al.* (2016)13	*		*	*	*	*	*	*	7
Kim JW. *et al.* (2014)14	*		*	*	*	*	*	*	7
Dinca O. *et al.* (2014)15	*		*	*	**	*	*	*	8
Valente NA. *et al.* (2019)16	*		*	*	*	*	*	*	7
Fernando C. *et al.* (2020)17	*		*	*	*	*	*	*	7
Mauceri R. *et al.* (2018)18	*		*	*	*	*	*	*	7

Table 3. Quality assessment using Cochrane Risk of Bias Tool of included RCT in systematic review

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Giudice A. *et al.* (2018)19	+	?	?	?	+	+	+

+ – low risk; ? – unclear risk.

- Mucosal integrity (no exposure of necrotic bone);
- Absence of residual infection;
- Presence of cutaneous fistulas;
- Re-intervention necessary to healing;
- Reduction of pain-visual analogue scale (VAS) score evaluation;

Surgery was performed by elevating muco-periosteal flap, removing necrotic bone, according to clinical parameters (altered structure, colour, bone bleeding) and wound closure was performed by tension-free suture. In experimental group surgical defect was covered with PRF membranes before suturing.

Significant difference (P<0.05) between groups was observed at T1 (1month) when evaluating mucosal integrity – meaning a faster wound closure in PRF group and decreased risk of infection in surgical site. The same results were seen when absence of infection was measured – 87.5% of PRF treated patients had reduced swelling 1 month after surgery, versus 60.9% in control group (P<0.05). A lower necessity for re-intervention was significantly lower in PRF group (P<0.05). It was also noted that VAS score was significantly lower in PRF group and patients taking high-dose drugs showed significant improvement in their quality of life with the use of PRF after surgery compared with control group.

In a Cohort study of Kim and others (14) with 34 patients, a success rate of 94% is achieved using resecting necrotic bone, irrigating with antibiotics and application of PRF with primary closure. Patient's response to treatment was recorded at 1 and 4 months postoperatively until complete resolution, which was defined by no exposed or necrotic bone at site, full coverage by mucosa and no pain. Delayed resolution was considered when necrotic bone was present at 1 month but resolved completely by 4 months. Seventy seven percent showed complete resolution at 1 month, 18% had delayed resolution. Similar success results were observed in other studies: 93% (13), 100% (15, 17). The lowest percentage observed was 73.3% (16).

Table 4. Studies characteristics

Study	No. of patients	Study design	ONJ stage	Patients mean age (years)	Drug therapy	Duration (months)	ONJ initiation	Treatment protocol	Follow up (months)	Success rate
Norholt SE. *et al.*, 2016 (13)	15	Cohort	2 (13) 3 (2)	68.5	Alendronate (5) Denosumab (4) Zoledronate (4) Ibandronate (1) Pamidronate (1)	High-dose mean 34 (15-73) Low-dose mean 126 (48-240)	Extraction (11) Prosthesis (3) Spontaneous (1)	Curettage PRF	7-20	93%
Kim JW. *et al.*, 2014 (14)	34	Cohort	1 (7) 2 (21) 3 (6)	71±13	Alendronate (19) Risedronate (8) Pamidronate (4) Zoledronate (3)	Median 78 (21-92)	Extraction (23) Spontaneous (5) Implantation (4) Prosthesis (2)	Curettage ABI L-PRF	6	94%
Dinca O. *et al.*, 2014 (15)	10	Cohort	2 (10)	59±15	Zoledronate (7) Ibandronate (3)	-	Extraction (10)	Curettage PRF	1	100%
Valente NA. *et al.*, 2019 (16)	15	Cohort	0 (1) 1 (4) 2 (9) 3 (1)	64	Zoledronate (5) Denosumab (4) Ibandronate (3) Alendronate (3)	-	Spontaneous (6) Extraction (5) Prosthesis (3) Implantation (1)	AB (1) Curettage L-PRF (13) Sequestrectomy L-PRF (1)	6-74	73.3%
Fernando C. *et al.*, 2020 (17)	11	Cohort	2 (11)	67.7±14.6	Alendronate (11)	Mean 57.6±14.7 (36-84)	Implantation (10) Extraction (1)	Curettage PRF	12-36	100%
Mauceri R. *et al.*, 2018 (18)	10	Cohort	1 (6) 2 (4)	75.2±5.94	Zoledronate (9) Ibandronate (1)	Mean 31.8±25.76	-	Curettage/ Sequestrectomy (laser) PRP	12	80%
Giudice A. *et al.*, 2018 (19)	47	RCT	2 (27) 3 (20)	74.7±6.5	Zoledronate (26) Alendronate (10) Denosumab (10) Ibandronate (1)	-	-	Curettage PRF (24) / Curettage (23)	12	PRF 95.8% Non-PRF 91.3%

ABI – antibiotic irrigation; AB – antibiotics.

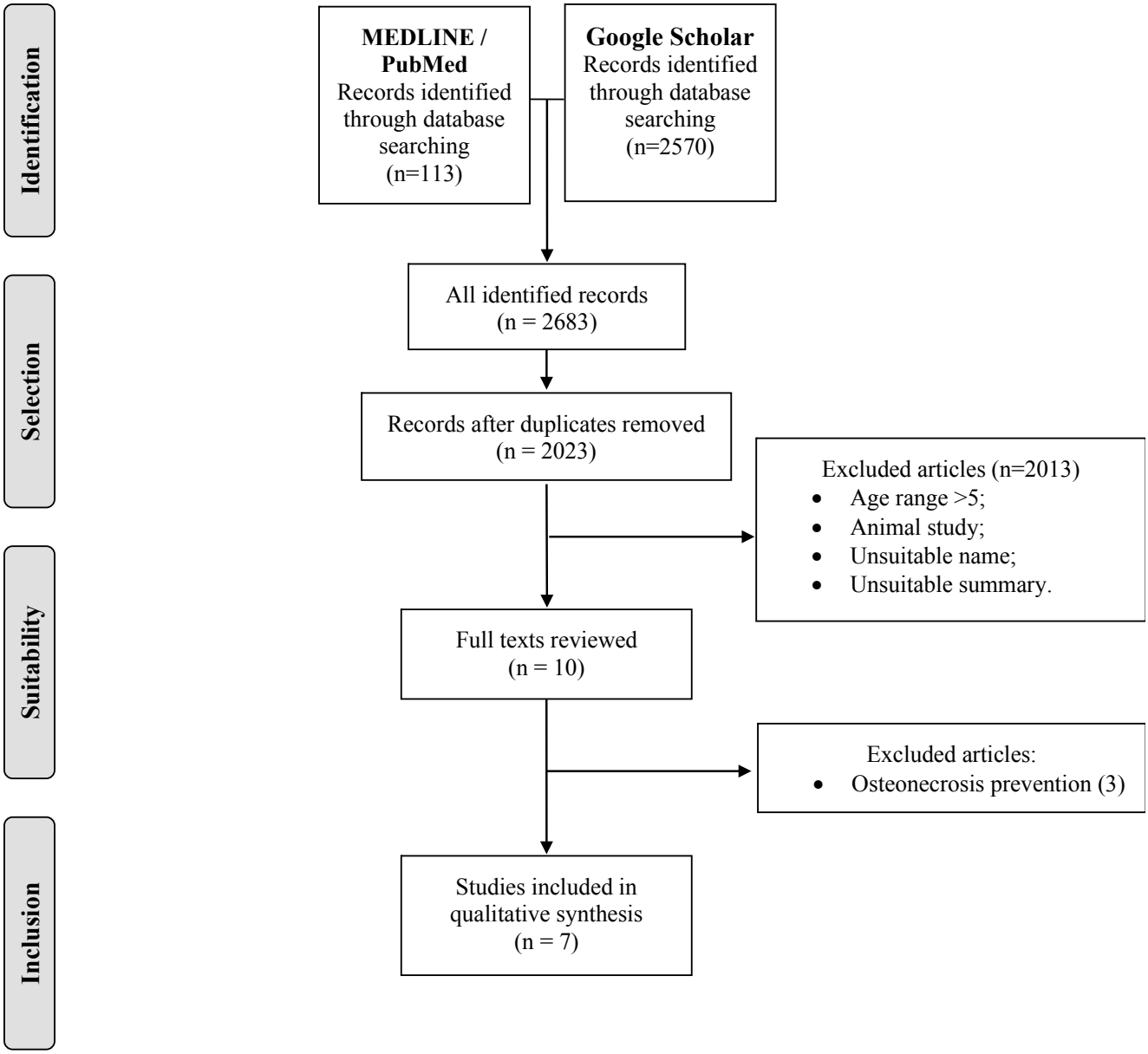

Fig. Teeth sectioning process with device Buehler "IsoMet Low Speed Saw" (on the left); a tooth section on the right

A novel treatment option was used to treat osteonecrosis in a cohort study of 10 patients who were treated with Er,Cr:YSGG laser and application of PRP instead of conventional surgery. Eighty percent of patients had a clinical improvement, although this was achieved only 12 months after surgery (18).

DISCUSSION

The goal of MRONJ surgery is to preserve quality of life and reduce pain as soon as possible with minimally invasive surgery approach. Although a fairly high success rate is seen in the studies, a fair number of patients improve only after a several months. The American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper concludes that a conservative approach including local debridement and disinfection with antimicrobial solutions or systematic antibiotic treatment should be the first choice of treatment (3). As seen from this review in moderate and advanced stages of MRONJ, conservative treatment is not successful and combined surgical approach should be used.

It is worth mentioning that only one study performed a C-terminal telopeptide test (CTX) on patients before performing surgery, although it is recommended to avoid surgical procedures when the value is lower than 150 pg/ml (20-23). It is also important to understand, that a significant association between MRONJ stage and treatment outcome exists – the worse the stage of MRONJ, the worse the response to treatment is (14).

Keeping in mind that up to this day a unanimous

treatment protocol doesn't exist, it is important to pay more attention to prevention of MRONJ. As the current researches show very good healing outcomes after surgical procedures using platelet concentrates (24-26), it expands use of APCs even before MRONJ develops.

CONCLUSION

The published data is not sufficient to confirm a specific treatment protocol although the published results are promising. More prospective randomized controlled clinical trials are required in order to evaluate the effectiveness of APCs for treatment of MRONJ.

CONFLICT OF INTERESTS

All authors declare no conflict of interests.

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