MRONJ INCIDENCE AFTER MULTIPLE TEETH EXTRACTIONS IN PATIENTS TAKING ORAL BISPHOSPHONATES WITHOUT "DRUG HOLIDAY": A RETROSPECTIVE CHART REVIEW

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SUMMARY

Introduction. The present retrospective chart review registered Medication-Related Osteonecrosis of the Jaw (MRONJ) occurrence after multiple adjacent teeth extractions in patients taking oral bisphosphonates (BPs) for osteoporosis for at least 3 years without "drug holiday".

Methods. Data from subjects ≥ 50 years old, requiring ≥ 2 tooth extractions of adjacent teeth, treated with oral BPs for osteoporosis for at least 3 years, who underwent multiple adjacent teeth extractions with a 12 months follow-up, at the Complex Operating Unit of Odontostomatology, Azienda Ospedaliero-Universitaria San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy, were included in the study.

Tooth extractions were planned in case of residual roots, destroying tooth decays, dental fractures and severe endodontic and periodontal infections. No oral BPs suspension was considered. Surgeries were performed by a single expert operator as a part of the standard clinical procedure. Follow-up consisted of weekly controls for the first month after extractions and monthly recalls for the next 11 months.

Results. Data from 58 patients charts accounting for 123 teeth extractions were included in the survey. No MRONJ development was registered.

Discussion and conclusions. Besides the positive observation, higher evidence level studies should be conducted on wider samples to better estimate MRONJ risk in osteoporotic patients assuming oral BPs without drug holiday and undergoing teeth extractions.

Key words: osteoporosis, medication-related osteonecrosis of the jaw, tooth extraction.

Objective

Osteoporosis currently affects about 200 million people and its prevalence is expected to increase in the future in relation to the aging of the population (1).

Among pharmacological agents prescribed to treat osteoporosis, bisphosphonates (BPs) are the most common, being effective in decreasing primary fragility fractures risk by 70% (2).

Adverse effects reported for oral BPs intake are: hypocalcemia, influenza-like symptoms, dysphagia and esophagitis, uveitis and episcleritis (3, 4), together with atypical femoral fractures and Medication-Related Osteonecrosis of the Jaw (MRONJ) (3, 5).

MRONJ is defined by the American Association of Oral and Maxillofacial Surgeons as the presence of exposed bone in the maxillofacial region lasting more than 8 weeks, in absence of previous history of radiation and of apparent metastatic disease of the jaws, with cuncurrent or previous treatment with antiresorptive agents (6). In addition, non-exposed MRONJ forms have been described, charactherized by oral and/or facial fistulae, pain, swelling and pathologic fractures (7).

MRONJ development has been related to dento-alveolar surgery, especially teeth extractions, considered as triggering factors (8, 9).

Because of the high prevalence of osteoporosis in the western population (1) and the actual consequent widespread BPs prescription (6), dentists and oral and maxillofacial surgeons commonly deal with a discrete number of osteoporotic patients under oral BPs therapy.

The present retrospective chart review registered MRONJ occurrence after multiple adjacent teeth extractions in patients taking oral BPs to treat osteoporosis for at least 3 years without “drug holiday”.

Methods

A retrospective chart review of subjects under oral BPs, undergoing multiple adjacent teeth extractions was conducted.

Consecutive patients undergoing teeth extractions as a part of the standard clinical procedure, between January and December 2017, at the Complex Operating Unit of Odontostomatology, Head and Neck Clinical Department, Azienda Ospedaliero-Universitaria San Giovanni di Dio e Ruggi d’Aragona, Salerno, Italy, were considered.

The survey was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the local Ethical Committee (Protocol n. 34/2013 on May 6, 2013 confirmed by the resolution # 776 Aug 6, 2014).

Data from subjects ≥ 50 years old, requiring ≥ 2 tooth extractions of adjacent teeth, treated with oral BPs for osteoporosis for at least 3 years were collected.

Teeth extractions occurred for residual roots, destroying tooth decays, dental fractures and severe endodontic and periodontal infections without oral BPs suspension.

As a part of the standard clinical routine, patients were prescribed professional oral hygiene procedures in advance and 0.2% chlorhexidine mouth rinses (twice a day, 1 week before surgery and until complete mucosal healing).

Oral Amoxicillin, 3 g 1 hour prior to teeth extractions and 2 g per day for the following 15 days, or oral Azithromycin, 1 g per day, for subjects allergic to penicillin, was also prescribed.

Surgical protocol, performed by a single expert operator, consisted of: mechanical extra- and intra-oral antisepsis with 0.2% chlorhexidine immediately before surgery (10); careful multiple adjacent teeth extractions, divided for sextants, under regional or local anesthesia with 3% mepivacaine; smoothening of the residual sharp bone

edges, post-extractive sockets curettage and irrigations with 0.2% chlorhexidine in a 10 ml disposable syringe; mucoperiosteal flap preparation with relieving incisions and 3-0 silk suture placement; intra-oral disinfection with 0.2% chlorhexidine after surgery.
Patients were recommended to have fresh and soft diet for at least two days and not to wear dentures until complete wound healing.
Follow-up consisted of weekly controls for the first month after extractions, with suture removal 14 days after surgery, and monthly recalls for the next 12 months.
The occurrence of exposed bone, swelling, fistulae and pathologic fractures in the post-extractive sites were eventually registered.

Results

Data from 58 consecutive patients requiring teeth extractions and under oral BPs for at least 3 years, were considered. Fifty-six were females and 2 males, between 52 and 89 years of age (mean age: 70,5). Fifty-one subjects resulted under alendronate, while the remaining 7 under other oral BPs; oral BPs intake duration before teeth extractions ranged from 37 to 65 months (mean 51 months) (Table 1).
A total of 123 teeth were extracted.
All 58 patients resulted treated successfully.
The follow-up period ranged from 12 to 17,8 months.
No occurrence of bone exposure, fistulae, swelling and pathologic fractures in the post-extractive sites, were registered.

Conclusion

In the present retrospective chart review of subjects assuming oral BPs and undergoing multiple adjacent teeth extractions, 51 out of 58 patients resulted under alendronate therapy, one of the most popular medication, as already pointed out by other Authors (11), who reported the prescription of this drug in almost the 90% of the observed osteoporotic patients.
No occurrence of clinical evidence of MRONJ, defined as bone exposure, fistulae, swelling and pathologic fractures in the post-extractive sites, was registered in the present survey, notwithstanding the assumption of oral BPs for at least recent 3 years and not “drug holiday” establish-

Table 1 - Patients distribution for age, gender, BPs type and therapy duration, comorbidities.

		Patients (n.)
Gender	Males	2
	Females	56
Age	52-60	12
	61-70	31
	71-80	13
	81-89	3
Oral BP type	Alendronate	51
	Others	7
Oral BP therapy duration	37 - 46 months	48
	47 - 56 months	8
	57 - 65 months	2

ment. Such a finding is in line with Lo et al. results (12), who reported a increased MRONJ incidence, up to 0.21% after dental procedures in patients who had earlier assumed oral BPs for more than 4 years. However, regarding the "drug holiday", Otto et al. already highlighted the long-term persistence of BPs anti-resorptive effects and consequently the usefulness of short-term drug suspension (13).

The reported clinical routine might contribute to minimize the risk of MRONJ development: no anesthetic intraligamentous infiltrations to avoid possible negative effects on mucosal healing (14); residual sharp bone edges removal and complete primary wound closure, recommended by Heufelder et al. (15) and Voss et al. (16) to reduce MRONJ re-occurrence, through mucoperiosteal flap preparation with relieving incisions and stable suture, soft diet and dentures disuse up to complete mucosal healing, as also described by Matsumoto et al. (8); extra- and intra-oral disinfection and post-extractive alveolous irrigation with 0.2% chlorexidhine preferred for the non cationic, irritating, long-lasting antiseptic activity, and wound healing stimulating effect (17), to povidone iodine, whose antimicrobial activity is not resistant to oral fluids and blood.

On this vein, present report seems comparable with the results of Kunchur et al. (18), who described only one case of MRONJ development out of 194 patients assuming oral BPs, thus estimating such a risk in osteoporotic patients under BPs after tooth extraction in about 0.5%, and with Ruggiero et al. (6) results, estimating this risk as 100 times lower compared to cancerous patients undergoing anti-resorptive therapies.

Present report is in agreement with the data by Otto et al. (13), Mozzati et al. (14), Heufelder et al. (15), outlining that tooth extraction was not associated with MRONJ development in osteoporotic patients assuming oral BPs, contrary to previous findings that considered tooth extraction as a precipitating event in about 50-60% of MRONJ cases.

Moreover, in the present chart review, teeth extractions were due not only for residual roots, destroying tooth decays and dental fractures, but also for severe endodontic and periodontal infections, as suggested by Saia et al. (19) and Kang et al. (20). These Authors reported that already existing jaws endodontic and/or periodontal infections could be responsible by themselves of MRONJ development, even before tooth extraction (19), possibly because of the acid inflammatory environment, enhancing BPs (particularly nitrogen-containing ones) cytotoxic effect, as reported by Otto et al. (13). These evidences could overturn the common recommendation to avoid dento-alveolar surgery in patients exposed to BPs, and may even lead to consider compromised teeth extraction in infective extractive sites as a preventative measure, rather than a risk factor, for MRONJ development (8), especially in association to pre- intra- and post-operative procedures to reduce inflammatory environment and avoid mucosal lesions (and consequent bone exposure risk).

Higher evidence level studies should be conducted on wider study samples to better estimate MRONJ risk in osteoporotic patients assuming oral BPs without drug holiday and undergoing teeth extractions and further studies are needed to explore the role of teeth extractions in MRONJ etiopathogenesis, on one side, and on MRONJ prevention, on the other side.

Conflict of interest statement

All Authors declare no actual nor potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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