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When not to go for tooth extraction in people on bisphosphonates – A prospective clinical study.

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Abstract *:Invasive dental procedures including tooth extraction are considered one of the most crucial risk factors for Bisphosphonate related osteonecrosis of the jaw (BRONJ). But sometimes the tooth cannot be salvaged due to poor prognosis. Ultimately the practitioner is in a dilemma whether to go for extraction or not. A lot of literature has been written about the methods to minimize the risk of developing BRONJ in an extraction patient. But very limited studies are there to stratify which patients can land in a complication. This study is based on 29 patients undergoing 45 extractions using different bisphosphonates for various medical conditions. In all patients, extraction sockets showed wound closure without bone exposure within minimum 4 weeks, followed by normal epithelization within 6 weeks after extraction except for 2 cases in which established BRONJ developed. However, 4 patients showed delayed healing with bone exposure in sockets even 8 weeks after extraction ultimately with proper soft tissue coverage. One observation could be made that all the established BRONJ cases or delayed healing were those with multiple myeloma and steroid intake with IV zolendronate as the BP used. The delayed healing cases where also those of IV zolendronate and multiple myeloma cases. This study though small concluded that primary bone disease are at increased risk for developing BRONJ than bone metastasis.*

Keywords *– BRONJ, zolendronate, extraction, myeloma*

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I. INTRODUCTION

Review papers and recent retrospective studies and several risk factors have been identified and discussed which are associated with BRONJ [1, 2, 3,4]. Major risk factors are a history of recent dental extractions, duration of bisphosphonates (BP) treatment, and the type of the bisphosphonates used. The majority of the reported BRONJ cases have a history of recent dentoalveolar surgery. Thus maintaining an optimal good health and avoiding extractions are important. However, spontaneous lesions may also occur in mucosal sites such as dentate or edentate areas or in areas that are covered by prosthesis. The phenomenon of the appearance of spontaneous cases of BRONJ can be explained by the fact that, the "metabolically damage" done by the treatment with bisphosphonates, jaw bones remain more susceptible to even minor causative factors caused by a trivial prosthetic trauma [1, 4].

Having said all this sometimes the extraction becomes mandatory and the dentist is in a fix whether to go ahead with extraction or not. So this short study was done to know which subset of patients taking BP's can give the patient and the practitioner a real trouble.

II. Patients And Methods

Twenty nine patients treated with BPs were prospectively included in this study. Patients were treated at the Oral Surgery department in Government Dental College And Hospital, Srinagar from year 2011 to 2013. Consent was obtained from the ethical committee and all patients that were included gave informed consent. Patients under the BP treatment, were informed about the possible consequence of dental extraction and all provided with written informed consent sheet before enrollment, in accordance with the "Declaration of Helsinki". At their first visit, data of the patients' were recorded in a clinical file which included information on gender, age, presence of any systemic disease, and type of drug used (Table 1).

Inclusion criterias included

1) Patients above 18 years old who used oral BPs for at least more than a year and intra venous BP's at least one dose BP within 3 years before extraction.

2) The patient who is willing to be part of the study, and
3) No clinical signs of BRONJ during the first visit.

Exclusion criterias were

1) Poor oral hygiene.
2) Transalveolar extraction cases.
3) Grade III mobile teeth.
4) Pregnant or breast-feeding women ,and
5) Confirmed or suspected hypersensitivity to any medication used.

II A: Technical Procedures

Routine radiography, to rule out complicated root morphology or a periapical lesion, was done. Two weeks before the tooth extraction, each patient underwent a root scaling and oral hygiene instructions. The evening before surgery, systemic antibiotic therapy with amoxicillin/ clavulanate potassium 625 tablets (every 8 hr) was commenced. Extractions were performed by the same oral surgeons. Inferior nerve anesthesia was achieved by using 2% lidocaine HCl and epinephrine 1:80,000. Tooth luxation and/or avulsion were performed using appropriate instruments. To avoid a delay in postoperative healing minimal osteoplasty of the alveolar ridge and sharp surfaces was done. Any exposed bone was covered. A 3-0 polyamide cross-suturing technique (figure 8) was used to close the wound. Standard postoperative instructions were given to patients and instructed to avoid brushing the teeth in the treated area and to gently clean the extraction wound by using a gauze soaked with 1.5% hydrogen peroxide TID daily for 2 weeks. A semisolid, cool diet for the first day was suggested. Hot food and rinsing and food were avoided for atleast 24 hours post- procedure. Oral hygiene procedures were re-established 3 days after procedure.
Patients were a followed-up for at least 3 months or till soft tissue healing was seen.

II B: Study Variables And Outcome Data

To confirm secondary healing of the sockets, follow up visits were scheduled at 1 week, 1month, 2 month and 3 months or till soft tissue coverage of the socket.

III. Results: Table (1)

We performed an audit of 45 extractions in 29 patients treated with BP's and evaluated their postoperative courses on follow ups for 3 months or when soft tissue coverage of the socket as noted (prospective study). BP's were administered to 12 patients with osteoporosis (4%), 7 patients (24%) with multiple myeloma, 5 patients (17%) with breast cancer, 5 patients (17%) with prostate cancer (Table 2). Also 5 (17%) patients were also receiving steroids, 7 patients (24%) had diabetes mellitus (DM). In all patients, extraction sockets showed wound closure without bone exposure within minimum 4 weeks, followed by normal epithelization within 6 weeks after extraction except for 2 cases in which established BRONJ developed. However, 4 patients showed delayed healing with bone exposure in sockets even 8 weeks after extraction ultimately with proper soft tissue coverage. One observation could be made that all the established BRONJ cases or delayed healing were those with multiple myeloma and steroid intake and zolendronate as the BP used in IV form and diabetes cases. The delayed healing cases where those of IV zolendronate and multiple myeloma cases.

Table 1. Patients primary diseases and bisphosphonates received (n = 29 patients)

S no.	OPD No	Sex	Age	Primary disease	BP used	Route	Duration	Socket healing time (weeks)	BRONJ
1	4189	M	53	MULTIPLE MYELOMA	ZOLENDRONATE	I V	3 YEARS	nil	Established
2	7343	F	48	OSTEOPOROSIS	PAMIDRONATE	PO	2 YEARS	4	Not Developed
3	8516	M	48	MULTIPLE MYELOMA	ZOLENDRONATE	I V	6 MONTHS	15	Not Developed
4	1785	F	76	OSTEOPOROSIS	PAMIDRONATE	PO	1 YEAR	8	Not Developed
5	1804	M	80	OSTEOPOROSIS	IBANDRONATE	PO	2 YEARS	7	Not Developed
6	111146	F	35	BREAST CA	PAMIDRONATE	PO	2 YEARS	3	Not Developed
7	113828	F	39	OSTEOPOROSIS	IBANDRONATE	PO	1 YEAR	4	Not Developed
8	127881	F	76	MULTIPLE MYELOMA	ZOLENDRONATE	I V	1 YEAR	14	Not Developed
9	128141	M	61	MULTIPLE	ZOLENDRONATE	I V	6	9	Not Developed

				MYELOMA			MONTHS		
10	130815	M	53	PROSTATE CA	ZOLENDRONATE	I V	3 YEARS	9	Not Developed
11	131763	M	58	PROSTATE CA	ZOLENDRONATE	I V	2 YEARS	8	Not Developed
12	133945	M	48	OSTEOPOROSIS	IBANDRONATE	PO	3 YEARS	5	Not Developed
13	140696	F	75	BREAST CA	PAMIDRONATE	PO	1 YEAR	4	Not Developed
14	141027	M	61	PROSTATE CA MULTIPLE	PAMIDRONATE	PO	2 YEARS	5	Not Developed
15	148597	M	52	MYELOMA	ZOLENDRONATE	I V	3 YEARS	14	Not Developed
16	156982	F	70	BREAST CA	PAMIDRONATE	PO	2 YEARS	5	Not Developed
17	156486	F	39	OSTEOPOROSIS	IBANDRONATE	PO	1 YEAR	4	Not Developed
18	167838	F	53	BREAST CA	PAMIDRONATE	PO	5 YEARS	6	Not Developed
19	173230	F	42	OSTEOPOROSIS MULTIPLE	IBANDRONATE	PO	4 YEARS	6	Not Developed
20	177675	F	48	MYELOMA	ZOLENDRONATE	I V	2 YEARS	nil	Established
21	64390	F	52	OSTEOPOROSIS	IBANDRONATE	PO	3 YEARS	4	Not Developed
22	173855	M	38	OSTEOPOROSIS	IBANDRONATE	PO	4 YEARS	4	Not Developed
23	169271	M	60	OSTEOPOROSIS	IBANDRONATE	PO	2 YEARS 6	3	Not Developed
24	189321	M	78	PROSTATE CA MULTIPLE	PAMIDRONATE	PO	MONTHS 1.5	3	Not Developed
25	194044	F	67	MYELOMA	ZOLENDRONATE	I V	YEARS	9	Not Developed
26	195619	M	55	OSTEOPOROSIS	PAMIDRONATE	PO	4 YEARS	3	Not Developed
27	207767	M	60	PROSTATE CA	ZOLENDRONATE	I V	1 YEAR 5.5	15	Not Developed
28	202009	F	65	OSTEOPOROSIS	IBANDRONATE	PO	YEARS 4.5	5	Not Developed
29	853	F	72	BREAST CA	PAMIDRONATE	PO	YEARS	6	Not Developed

Table 2: Patients primary diseases (n = 29 patients)

Primary disease	Number of patients (percentage).
Osteoporosis	12 (41)
Multiple myeloma	7 (17)
Breast cancer	5(7)
Prostate cancer	5 (7)

Table 3: Bisphosphonates received (n = 29 patients)

Bisphosphonates used	No of cases(percentage).	Route of administration
Zoledronic acid	10(34.48)	10 iv
		0 po
Pamidronate	10 (34.48)	10 po
		0 iv
Ibandronate	9 (31.04)	9 po
		0 iv

IV. Discussion

Bisphosphonate related osteonecrosis of the jaws (BRONJ) is defined as a side effect of the inhibition of osteoclasts in which exposed and necrotic bone persisting for more than 8 weeks occurs in the maxillofacial region, which could be related to current or previous treatment with BPs, with no history of radiotherapy to the head and neck area [5]. The administration of oral and IV nitrogen-containing BPs (NBPs) are more frequently associated with development of BRONJ than the non-nitrogen-containing BPs [6]. This frequency seen in in cancer patients is (94%) for IV BPs while as only 6% of cases patients receiving oral BP .[7]. Although both jaws (4.2 to 4.5%) can be involved but the mandible is more frequently involved (68.1 to 73%) than maxilla (22.5 to 27.7%). [8,9] And tooth extraction appears to be a major risk factor for the development of the BRONJ [10]. Howover what subset of extraction patients will end up in complications is to be determined.

First of all the medical bone condition for BP's are given has an important bearing on the complication as none of the osteoporosis cases developed a complication. Also none of the cases of the metastasis in bone in breast or prostate cancer developed a complication after extraction. Howover most cases of multiple myeloma did land up in a complication including two cases of established BRONJ. So primary bone disease cases taking BP's are at more risk of complication. The duration of bisphosphonates therapy is also an important factor which relates to the likelihood of developing BRONJ. In addition, the development of BRONJ was more frequent with more potent nitrogen-containing bisphosphonates, zoledronate, than their oral congeners.[11-17]

A recent prospective study assessed 252 patients who received bisphosphonates and BRONJ was diagnosed in 17 of them. In addition, this study showed that duration of IV bisphosphonate usage appeared to be the most important risk factor. [18] Here also in our study all cases with delayed socket healing or established BRONJ were on zolendronate with long duration of intake.

A variety of other etiological factors such as corticosteroid treatment, trauma, diabetes, may also show an adjuvant affect on wound healing of the jaw bones and as such be considered as possible cofactors.[19] So was true with our study also.

In summary, the fact that the majority of BRONJ cases are associated with the use of iv bisphosphonates for multiple myeloma and metastatic bone diseases suggests that patients with primary bone disease taking IV zolendronate for longer periods are at increased risk of developing delayed healing and/or BRONJ and as such extraction is to be avoided unless it is the only solution. Other cases with metastatic bone diseases or osteoporosis on oral BP's can be taken for extraction. So such cases should be handled with care with all possible precautions as established by authors from time to time as outlined in the postion paper of AAOMS. [20] However, more work on this topic with greater number of cases should be initiated.

V. Conclusion

Though the study was based on less number of cases to give a law yet the following conclusion could be drawn. Tooth extraction as a precipitating event is a common observation in the reported literature. The reported incidence of BRONJ is significantly higher with the IV preparations zoledronic acid than receiving oral bisphosphonates. And more in those subset of patients on BP's who take it for primary bone diseases like multiple myeloma as compared to those taking it for metastatic bone disease. As such extraction in this subset of patients should be avoided unless extremely important.

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