

Awareness of the Risk of BRONJ/ARONJ Amongst Dental professionals in KPK

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ABSTRACT

Objective: Osteonecrosis of the jaws is an established adverse side effect of nitrogen-containing bisphosphonates, also known as amino bisphosphonates. Since the first case reports in 2003, there has been an increased surge in the literature of osteonecrosis related to bisphosphonates. Despite the established risk, there is almost no evidence-based publications in Pakistan on awareness of GDPs regarding this complication. The aim of this study (the first of its kind), to investigate the degree of awareness of general dental practitioners treating patients receiving bisphosphonates/Antiresorptive Medications in the primary care sector of the possible risk of Bisphosphonate/Antiresorptives related osteonecrosis of the jaw (BRONJ/ARONJ).

Methods: A questionnaire with a covering letter was sent to general dental practitioners working in private practices and Hospitals based work places in KPK. The questionnaire was designed to maintain total anonymity of the practitioners. Out of 200 GDPs requested in KPK 93 answered questionnaire were returned. Chi-square test was used for categorical variables. A p value of less than 0.05 was considered as significant.

Results: Participant's response rate was 46.5%. 70% of respondents practiced in a mixed (Government hospitals + Private) setting. 100 % of respondents have come across the pharmaceutical term 'Bisphosphonates' or 'Antiresorptive' agents. 91/93 (98%) were also positive about being familiar with the indications for treatment with these agents. 92/93 were aware of a relationship between these agents and oral health. 50% were aware of current schemes/pathways/protocols which deal with patients on 'Bisphosphonates' seeking dental treatments. All the responses were statistically significant ($p=0.000$).

Conclusion: The study showed a noticeable awareness of risk of BRONJ/ARONJ amongst GDPs in KPK. 54% of respondents showed interest in receiving information packs or attending tutorials.

Keywords: ARONJ, BRONJ, GDPs

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BONJ) was first reported in 2003 by Marx et al. He defined bisphosphonate related osteonecrosis of the jaws as a condition which is characterized by bone exposure in the maxilla or mandible persistent for more than 8 weeks in a patient who is currently taking or taken previously a bisphosphonate and who has no radiation therapy history of the jaws (Marx et al 2003).

There is a surge in literature regarding BRONJ risks and a number of professional associations have come up with guidelines for management. It is unanimously agreed that prevention is the best approach in treating those patients who are taking BPs and appropriate prescription is the first step in prevention but beyond the scope of this article. This study focus on the awareness of General Dental Practitioners (GDPs) regarding Bisphosphonate/Antiresorptives related osteonecrosis of the jaw (BRONJ/ARONJ) in KPK.

Bisphosphonates are inorganic pyrophosphates analogues which has prolong inhibitory effects on osteoclast maturation and function therefore suppress bone resorption. (Fleisch, 2002, Coxon et al., 2008;). Bisphosphonates are administered intravenously as infusion or injection or orally as tablets. 50-70% of Bisphosphonate reach the bone if administered intravenously (Julia S et al 2012). Interavenously administered Bisphosphonates are used in patients with lung, prostate and breast cancers, or patients with primary osteolytic bone pathologies e.g multiple myeloma and paget's disease (Terpos et al.,

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2009; Coleman, 2006; Rosen et al., 2001). Bisphosphonates are used in tumour metastases and tumour-induced osteoporosis, which could be due to reduction in bone destruction. Oral Bisphosphonates have been heavily prescribed to osteoporosis patients, especially in postmenopausal women (Fratasi J E 2009).

Osteonecrosis of the jaw is not a common condition and has known systemic & local risk factors; Bisphosphonate increases all these risks (Vinod Patel et al 2011). Systemic factors include age, smoking, systemic diseases (anaemia, renal failure, obesity, diabetes), concurrent medication (chemotherapy agents, immunosuppressants and Bisphosphonate) while local factors include oral infections (periodontal and dental abscesses, poor oral hygiene, intraoral trauma and dentoalveolar surgery (Vinod Patel et al 2011). Risk-potential of different Bisphosphonates varies. Abu-Id et al reported that patients receiving intravenous therapy (Pamidronate or Zoledronate) for malignant disease and / or chemotherapy or current steroids history are high-risk patients. They also reported that patients taking oral Bisphosphonates (e.g. patients with non-steroids induced osteoporosis) and no history of chemotherapy or steroids have low risk of developing BRONJ (Abu-Id et al., 2008).

The aim of this study was to find out the extent of GDPs knowledge regarding BRONJ, confidence level in treating this group of patients and need for tutorials or further information on this topic.

Methods

This study involved General Dental Practitioners of the KPK's Mingora Swat, Batkhela Malakand and Peshawar region. A questionnaire with a covering letter was sent out to GDPs. Covering letter was for explaining the aim of the survey to the practitioners and inviting them to answer the questionnaire. Newly established Swat Dental College staff, Department of Dentistry at Hayat Abad Medical Complex and District Malakand GDPs were directly approached to participate and answer our questionnaire voluntarily. The questionnaire included 13 closed-end and related open-end questions and was designed to maintain total anonymity of the practitioner. The returned answered questionnaires were assessed and the answers were entered on Excel spreadsheets and analysed. Chi-square test was used for categorical variables. A p value of less than 0.05 was considered as significant. All the results were documented in the form of tables and figures. The questionnaire used in our study is given in table 1.

Table 1: Questionnaire used in our study

No	Question	Category
1	Are you currently a practicing	General Dental Practitioner
		Trainee Medical Officer
		Other
2	What is your current area of practice?	Private Practice
		Hospital Dental Surgeon
		Both
3	Have you ever come across the term 'Bisphosphonates' or 'Anti-resorptive' agents?	Yes
		NO
4	Are you familiar with its clinical indications?	Yes
		NO
5	Are you aware of Oral health relationship with 'Bisphosphonates'?	Yes
		NO
6	Are you aware of its any serious side effects?	Yes
		NO
7	If you are aware of its any serious side effects give detail	
8	Do you discuss those side effects/complications with your patients before providing your treatment?	Yes
		NO
9	Do you treat patients on 'Bisphosphonates' or do you refer them to specialist departments?	Treat
		Refer
		Both
		N A
10	Which cases would you consider referring to the specialist department & for what treatment?	

11	Have you ever read/received information/ attended any tutorials about the side effects/complications associated with treatment of 'Bisphosphonates' on the oral health of patients?	Yes
		NO
12	If not, which of the following would you be interested in receiving?	Information pack
		Tutorials
		Both
		NA

Results:

Are you currently a practicing * what is your current area of Practice

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	17.257 ^a	4	.002
Likelihood Ratio	24.931	4	.000
Linear-by-Linear Association	12.793	1	.000
N of Valid Cases	93		

The Chi-square significance is .002 and so there is strongly statistical significance between the Currently a practicing and What is your current area of Practice. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is very strong evidence of an association between Currently a practicing and What is your current area of Practice.

Are you currently a practicing * Have you ever come across the term Bisphosphonates or Anti Resorptive Agent ?

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.435 ^a	2	.009
Likelihood Ratio	4.775	2	.092
Linear-by-Linear Association	5.927	1	.015
N of Valid Cases	93		

The Chi-square significance is .009 and so there is statistical significance between Currently a practicing and Have you ever come across the term Bisphosphonates or Anti Resorptive. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is evidence of an association between Currently a practicing and Have you ever come across the term Bisphosphonates or Anti Resorptive.

Are you currently a practicing * Are you familiar with its clinical indications

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.435 ^a	2	.009
Likelihood Ratio	4.775	2	.092
Linear-by-Linear Association	5.927	1	.015
N of Valid Cases	93		

The Chi-square significance is .009 and so there is statistical significance between Currently a practicing and Are you familiar with its clinical indications. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is evidence of an association between Currently a practicing and Are you familiar with its clinical indications.

Are you currently a practicing * Are you aware of its Oral Health relationship with Bisphosphonates

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.435 ^a	2	.009
Likelihood Ratio	4.775	2	.092
Linear-by-Linear Association	5.927	1	.015
N of Valid Cases	93		

The Chi-square significance is .009 and so there is statistical significance between the Currently a practicing and Are you aware of its Oral Health relationship with Bisphosphonates. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is evidence of an association between Currently a practicing and Are you aware of its Oral Health relationship with Bisphosphonates.

Are you currently a practicing * Are you aware of its any serious side effects

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	2.276 ^a	2	.320
Likelihood Ratio	3.703	2	.157
Linear-by-Linear Association	1.910	1	.167
N of Valid Cases	93		

The Chi-square significance is .320 and so there is statistical insignificance between the Currently a practicing and Are you aware of its any serious side effects. In this table p value is greater than standard p value 0.05. that is way both the variable is statistical insignificant. Therefore, we accept our null hypothesis with 95% confidence and conclude that there is no evidence of an association between Currently a practicing and Are you aware of its any serious side effects.

Are you currently a practicing * If you are aware of its any serious side effects give detail

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	80.547 ^a	4	.000
Likelihood Ratio	53.030	4	.000
Linear-by-Linear Association	53.251	1	.000
N of Valid Cases	88		

The Chi-square significance is .000 and so there is strongly statistical significance between the Currently a practicing and If you are aware of its any serious side effects give detail. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is very strong evidence of an association between Currently a practicing and If you are aware of its any serious side effects give detail.

Are you currently a practicing * Do you discuss those side effects/complications with your patients before providing your treatment.

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	40.932 ^a	2	.000
Likelihood Ratio	52.212	2	.000
Linear-by-Linear Association	34.353	1	.000
N of Valid Cases	93		

The Chi-square significance is .000 and so there is strongly statistical significance between the Currently a practicing and Do you discuss those side effects/complications with your patients before providing your treatment. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is very strong evidence of an association between Currently a practicing and Do you discuss those side effects/complications with your patients before providing your treatment.

Are you currently a practicing * Do you treat patients on bisphosphonates or do you refer them to specialist department.

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	97.934 ^a	6	.000
Likelihood Ratio	109.587	6	.000
Linear-by-Linear Association	76.101	1	.000
N of Valid Cases	93		

The Chi-square significance is .000 and so there is strongly statistical significance between the Currently a practicing and Do you treat patients on bisphosphonates or do you refer them to specialist department. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is very strong evidence of an association between Currently a practicing and Do you treat patients on bisphosphonates or do you refer them to specialist department.

Are you currently a practicing * Which cases would you consider referring to the specialist department and for what treatment?

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	124.135 ^a	6	.000
Likelihood Ratio	109.676	6	.000
Linear-by-Linear Association	63.158	1	.000
N of Valid Cases	93		

The Chi-square significance is .000 and so there is strongly statistical significance between the Currently a practicing and Which cases would you consider referring to the specialist department and for what treatment. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is very strong evidence of an association between Currently a practicing and Which cases would you consider referring to the specialist department and for what treatment.

Are you currently a practicing * If not, which of the following would you e interested in receiving?

Chi-Square Tests			
	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	45.495 ^a	6	.000
Likelihood Ratio	56.616	6	.000
Linear-by-Linear Association	26.191	1	.000
N of Valid Cases	92		

The Chi-square significance is .000 and so there is strongly statistical significance between the Currently a practicing and If not, which of the following would you e interested in receiving. In this table p value is smaller than standard p value 0.05. that is way both the variable is statistical significant. Therefore, we reject the null hypothesis with 95% confidence and conclude that there is very strong evidence of an association between Currently a practicing and If not, which of the following would you e interested in receiving.

The questionnaire was sent to 200 GDPs in KPK.93 GDPs answered questionnaire were returned (response rate of 46.5%). All the respondent 93/93 (100%) were observed practicing. Majority 65/93 (70%) of the respondent were general dental practitioner. (Figure 1) 70% of respondents practiced in a mixed (Government hospitals+ Private) setting (Fig 2).100 % of respondents answered Yes 91/93 (98%) were also positive about being familiar with the indications for treatment with these agents (Fig 3). 92/93 were aware of a relationship between these agents and oral health.2/3 of respondents claimed they were happy to offer dental treatments to patients on Bisphosphonates, and 87% said they would only refer patients on IV bisphosphonates, difficult/multiple extraction and/or both figure 4 & 5.50% were aware of

current schemes/pathways/protocols which deal with patients on 'Bisphosphonates' seeking dental treatments. 50 out of 93 GDPs were interested in more information's in the form of tutorials or written information packs by post figure 6. Majority of the participants were able to specify BRONJ as serious complication in answer to the question Are you familiar with any serious side effects/complications related to treatment of patients on 'Bisphosphonates'? Knowledge and confidence of most of the practitioners is evident, most are aware of the relationship between 'Bisphosphonates' and the oral health of the patient. All the responses were statistically significant (p=0.000). The overall responses of different respondent to the questionnaire used in our study are given in table 2.

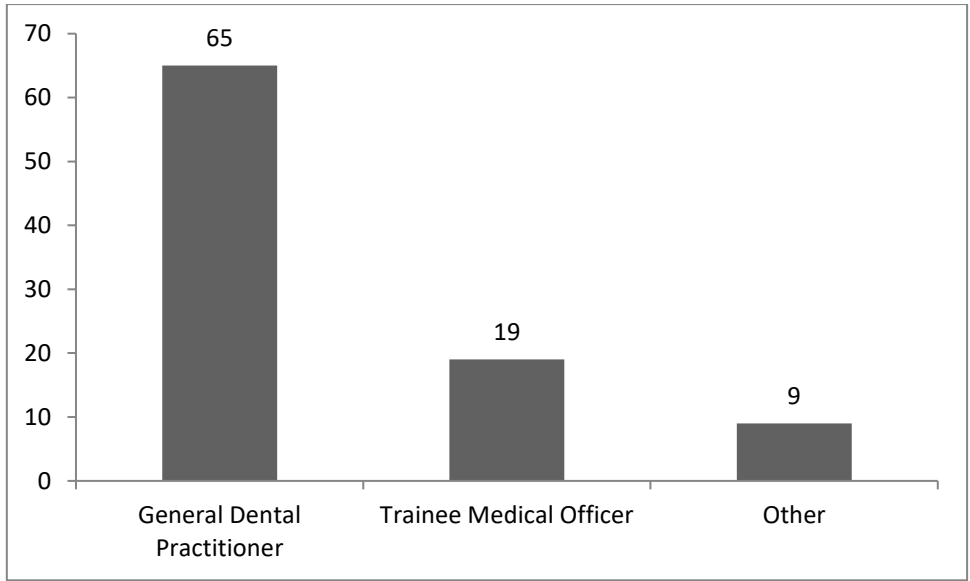


Figure 1: Practicing of different respondent

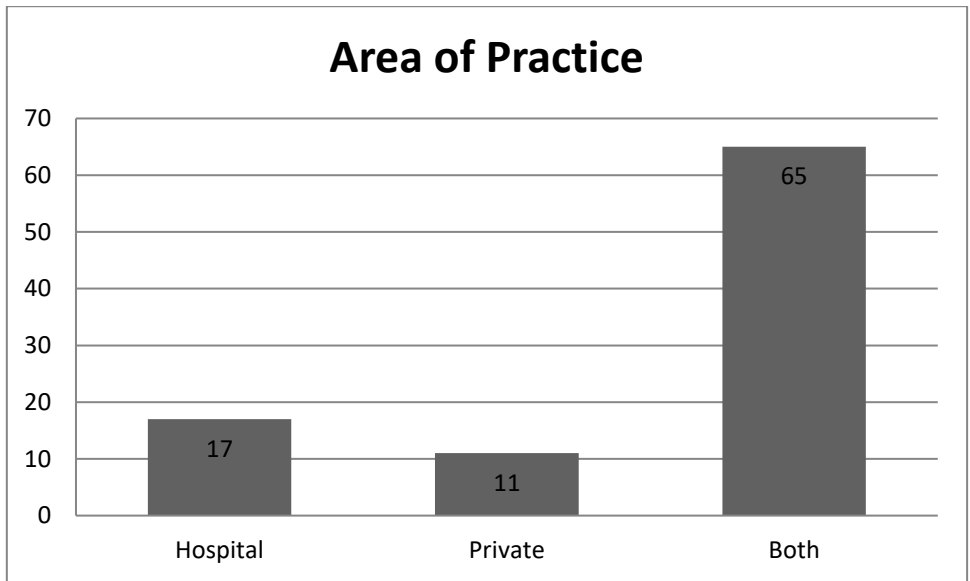


Figure 2: Area of practice of different respondent



Figure 3: Familiarity of the respondent with the clinical indications for treatment with bisphosphonates

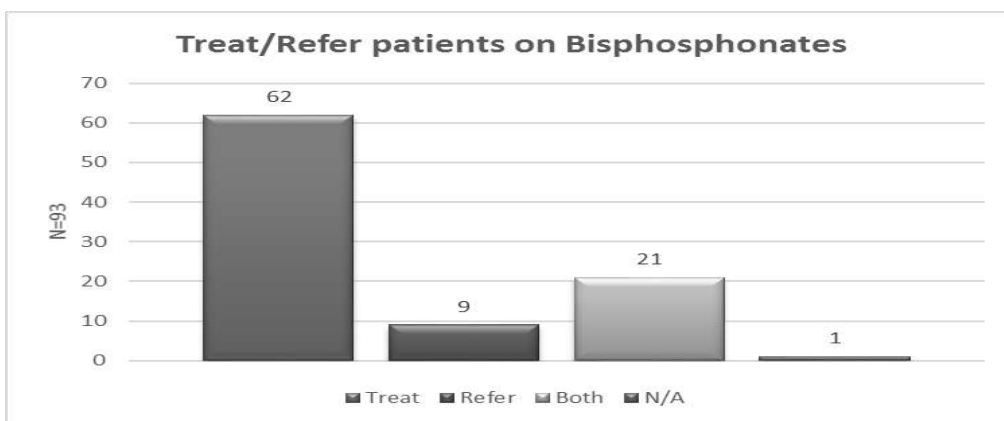


Figure 4: Response about treatment or referral of patients on bisphosphonates

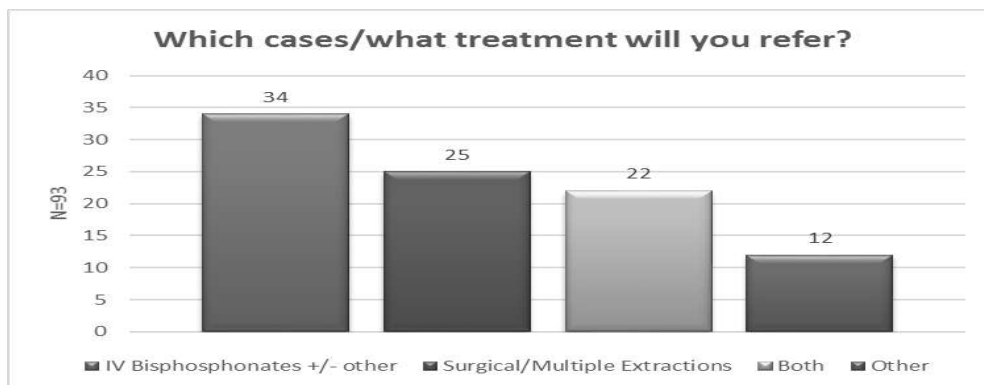


Figure 5: Response about referral of patients

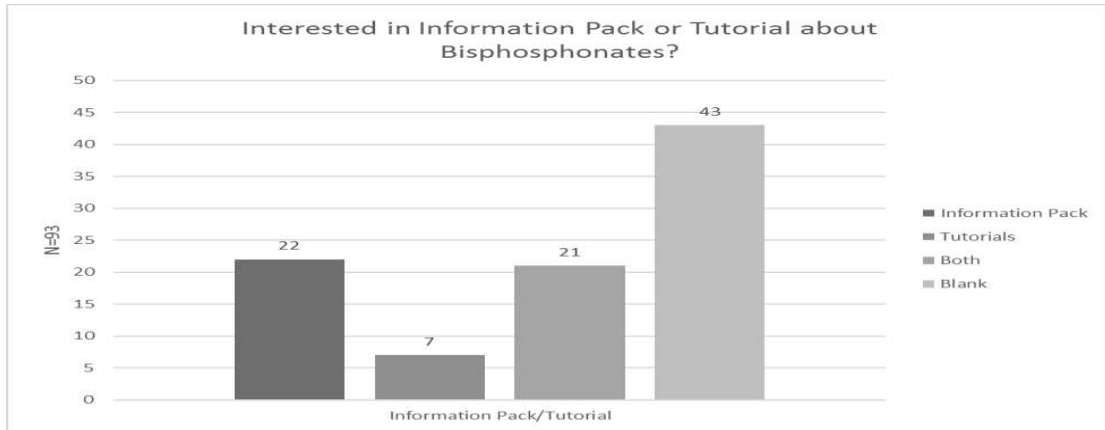


Figure 6: Respondent interested in information pack or tutorial about bisphosphonates

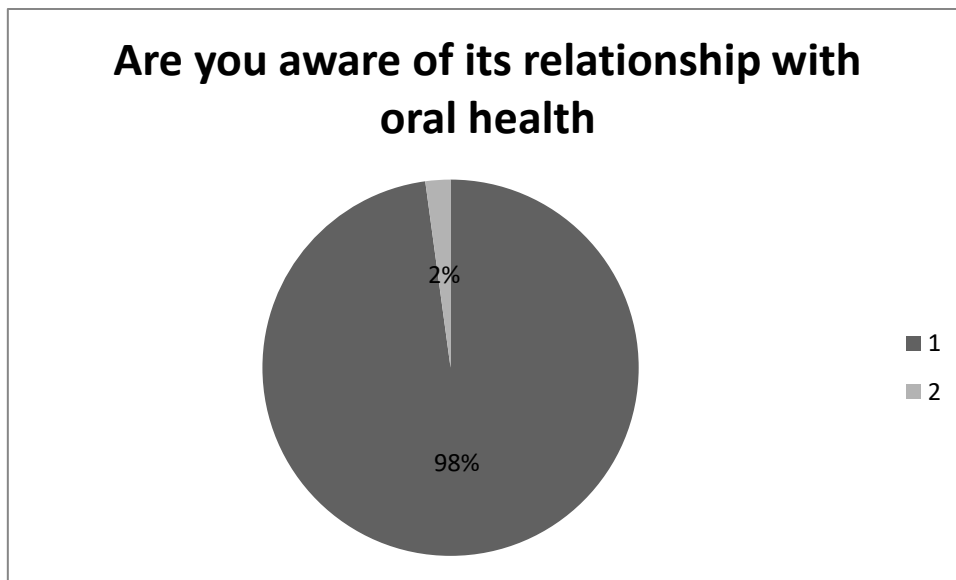


Figure 7: Knowledge of the respondent about the relationship between bisphosphonates and oral health

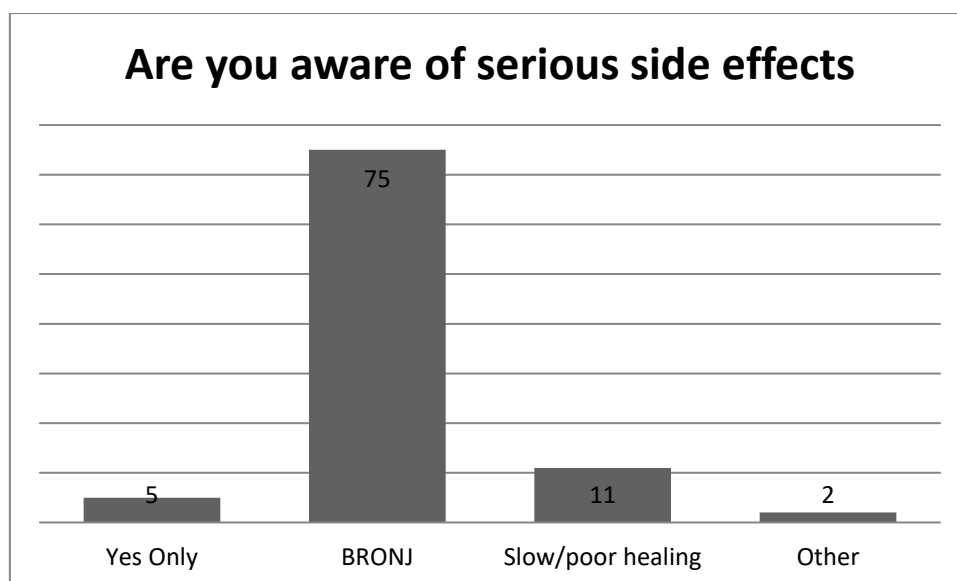


Figure 8: Awareness about side effects of bisphosphonates

Table 2: Responses of different respondent to the questionnaire used in our study

No	Question	Category	Responses	P value
1	Are you currently a practicing	General Dental Practitioner	65	0.000
		Trainee Medical Officer	19	
		Other	9	
2	What is your current area of practice?	Private Practice	17	0.000
		Hospital Dental Surgeon	11	
		Both	65	
3	Have you ever come across the term 'Bisphosphonates' or 'Anti-resorptive'agents?	Yes	92	0.000
		NO	1	
4	Are you familiar with its clinical indications?	Yes	91	0.000
		NO	2	
5	Are you aware of Oral health relationship with 'Bisphosphonates'?	Yes	92	0.000
		NO	1	
6	Are you aware of its any serious side effects?	Yes	5	0.000
		NO	88	
7	If you are aware of its any serious side effects give detail	BRONJ	75	0.000
		Slow/poor healing	11	
		Other	2	
8	Do you discuss those side effects/complications with your patients before providing your treatment?	Yes	47	0.000
		NO	46	
9	Do you treat patients on 'Bisphosphonates' or do you refer them to specialist departments?	Treat	62	0.000
		Refer	9	
		Both	21	
		N A	1	
10	Which cases would you consider referring to the specialist department & for what treatment?	IV bisphosphonates,	34	0.000
		difficult/multiple extraction	25	
		both	22	
		Others	12	
11	Have you ever read/received information/attended any tutorials about the side effects/complications associated with treatment of 'Bisphosphonates' on the oral health of patients?	Yes	93	0.000
		NO	0	

12	If not, which of the following would you be interested in receiving?	Information pack	22	0.000
		Tutorials	7	
		Both	21	
		NA	43	

Discussion:

In this study, GDPs awareness of the risks and side effects associated with Bisphosphonates was evaluated. We also evaluated GDPs confidence in treating the patients in primary and/or if needed referring them to tertiary care facilities. Treatment of BRONJ depends on clinical presentation and is generally considered difficult. It varies from conservative management to jaw resection and reconstruction (Alons et al., 2009). General Dental Practitioners role is of pivot importance when it comes to prevention of BRONJ. It is also necessary and mandatory for clinicians to explain possible risks, side effects and potential treatment difficulties to this group of patients. Periodontal therapy, endodontic treatments, and dental extractions should be executed before the start of Bisphosphonate (Leite et al., 2006; Hewitt and Farah, 2007; Estefania et al., 2006).

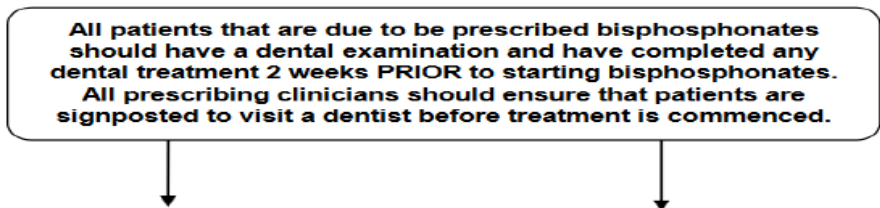
The response rate to the survey questionnaire was low but awareness amongst GDPs of the specifics of the risks associated with the treatment with Bisphosphonates/Antiresorptive agents is evident in the survey 54% of respondents showed interest in receiving information.

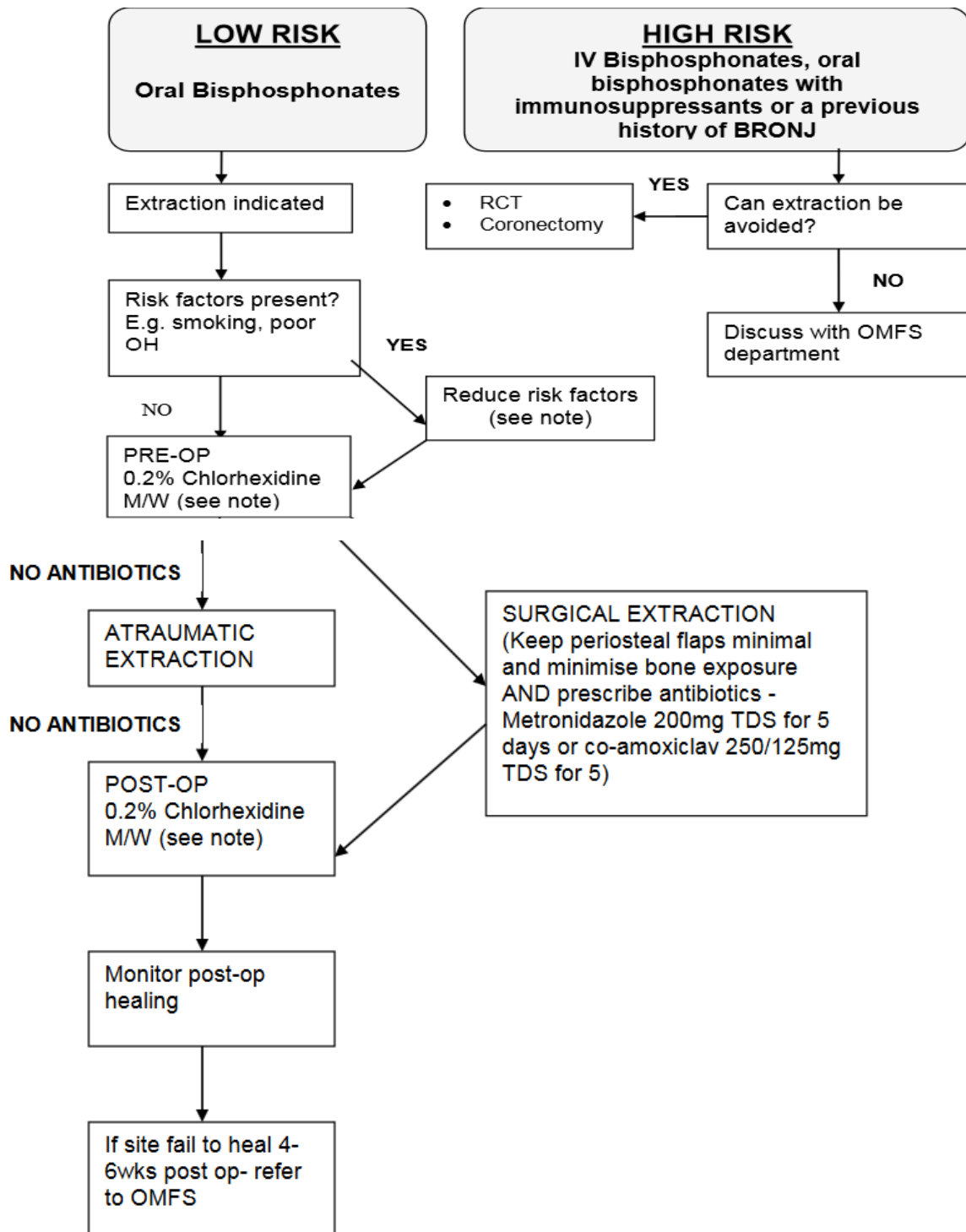
What the Dental practitioners needs to know: There is no supporting evidence that BONJ risk will be reduced if the patient temporarily, or even permanently, stops taking bisphosphonates prior to invasive dental procedures since the drugs may persist in the

skeletal tissue for years. If a patient has taken bisphosphonates in the past but is no longer taking them for whatever reason (i.e. completed or discontinued the course, taking a drug holiday), allocate them to a risk group as if they are still taking them. (University Hospitals of North Midlands NHS Trust (UHNM) www.england.nhs.uk/bisphosphonates-guidelines-2015 PDF)

Reduce risk factors: Whenever possible, patients should be encouraged and counselled to stop smoking. Oral hygiene and periodontal health should be improved prior to any surgical procedures. However, the unnecessary delay or avoidance of appropriate treatment cannot be supported and each case should be considered on its own merits. (www.england.nhs.uk/bisphosphonates-guidelines-2015 PDF)

Chlorhexidine mouthwash: All patients to rinse with Chlorhexidine mouthwash twice daily during the week before extractions are done. There is no evidence that pre-and post-operative antibiotics are effective in preventing BRONJ. Immediately before the extractions, the area should be irrigated/wiped with chlorhexidine. Use a atraumatic technique, and avoid raising flaps. Primary soft tissue closure should be achieved wherever possible. 24 hours post-operatively patients should rinse with Chlorhexidine twice daily for 2 months, and should be reviewed regularly to monitor healing. (www.england.nhs.uk/bisphosphonates-guidelines-2015 PDF)





Conclusion:

The study showed a noticeable awareness of risk of BRONJ/ARONJ amongst GDPs in KPK. Despite the low response, the survey showed interest in knowing more about the subject, which seems to have become common

knowledge amongst GDPs. The results of this survey should not be underestimated, as it samples the relative need to reach out to practitioners in the primary care sector with information about the condition and help in better planning of their postgraduate education agenda.

DECLARATIONS

Authors Contribution:

1. Main author is DrSuhailShahzad and this article is not submitted to any other journal. Study design and ethical approval was obtained accordingly.
2. DrTaran Kumar, DrKanwalllyas and Dr M Tariq were involved in data collection, feeding data and analyzing results. They also helped in writing up various sections of the article.

Conflict of Interest: No conflict of interest involved in this study.

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15. Dental Management of Patients Prescribed Bisphosphonates -Clinical Guidance January 2015 Authored by–Dept. of Oral and Maxillofacial Surgery, University Hospitals of North Midlands NHS Trust (UJNM) www.england.nhs.uk/bisphosphonates-guidelines-2015PDF)