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Research Article

Treatment Options of Giant Cell Granulomas of the Jaws

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Abstract

Background: Giant cell granulomas are benign osteolytic lesions of the jaws and are believed to be related to teeth. This study explores both surgical and adjunctive pharmacological therapy used in treatment of giant cell granulomas and presents the treatment options of giant cell granulomas of the jaws treated at The Leeds Teaching Hospitals NHS Trust.

Methodology: Our study was a retrospective cohort study. Eligibility criteria was a histologically confirmed giant cell granulomas (peripheral and central giant cell granulomas) with patient treated at The Leeds Teaching Hospitals NHS Trust from 2005-2017. Data collection was from the computerized hospital database. Surgery was carried out as the first line of treatment and in cases of recurrence further enucleation and curettage with pharmacological therapy. Pharmacological agents used as treatment of giant cell granulomas were intralesional steroids and calcitonin intranasal spray in two cases of recurrence followed by clinico-radiological monitoring of these patients.

Results: A total of 25 cases were treated during this period. In our study, 23 patients were treated by enucleation and curettage alone while 2 patients had further surgery with adjunctive pharmacological therapy - intralesional steroids and calcitonin intranasal spray. Age of presentation varies from 7 to 76 years with a mean age of 44.8 years. Sixteen patients [64%] presented at age 40 years and over while 16 [64%] of the 25 patients were male while 9 [36%] patients were females.

Conclusion: Our result was in variance to most studies which reported a female preponderance (2:1) and patient presentation in the first three decades of life.

Keywords: *Giant Cell Granulomas; Jaws; Enucleation; Recurrence; Pharmacological Treatment*

Introduction

Giant cell granulomas are benign osteolytic lesions of the jawbone of unknown aetiology [1]. They were first reported by Jaffe in 1953 when they had been called 'giant cell reparative granulomas.' The notion at that time was that these lesions only appeared in the jaws and are related to teeth and more frequently in females and were found in the third decades of life [2]. However there seems to be some controversies around the aetiology of these conditions, some regard them as benign tumours, reactive lesions, others call them inflammatory lesions, metabolic or as self- limiting lesions [3].

World Health Organisation (WHO) define these lesions as "localized benign but sometimes aggressive, osteolytic proliferation consisting of fibrous tissue with hemosiderin deposits and presence of osteoclast-like giant cells with reactive bone formation" [4]. They are infrequent but locally belligerent and destructive osteolytic lesions of osteoclastic origin that can be found in the head and neck region, especially in jaw bones. They occur more commonly in the mandible than maxilla [5]. In the mandible they can typically be seen in the body region, areas anterior to the first molars and affects patients under the age of 30 years [6].

Pathogenesis of giant cell granulomas are unknown, though local irritation was suggested as a risk factor to the development of these lesions. In addition, they originate from the connective tissue of the periosteum or from periodontal membrane [7]. These lesions are not a true neoplasm, but somewhat benign hyperplastic reactive lesion [8] in response to a stimulus producing a chronic process whereby an exaggerated repair occurs as granulation tissue and scar tissue following injury [9,10]. Also, it has been suggested that prolonged trauma can induce inflammation, with endothelial cells, and fibroblasts proliferation, granulation tissue formation and exhibits as tissue overgrowth termed reactive hyperplasia [10].

Surgery is regarded as the optimum and most widely accepted treatment for giant cell granulomas. Surgical techniques include enucleation and curettage, peripheral osteotomy with root planing of adjacent teeth [11]. Pharmacological agents such as intralesional steroids, calcitonin, desunomab and alpha interferon have been used as adjunctive therapy [1,12].

Aim of the Study

Our study report both surgical and pharmacological therapy used in treatment of giant cell granuloma especially when there is recurrence. We present the treatment options of 25 cases of giant cell granulomas of the jaws treated at The Leeds Teaching Hospitals NHS Trust.

Materials and Methods

Our study was a retrospective cohort study. Eligibility criteria was a histologically confirmed giant cell granulomas (peripheral and central giant granulomas) with patient treated at The Leeds Teaching Hospitals NHS Trust from 2005-2017. Data collection was from the computerized hospital database, Patient Pathway Manager (PPM+). The protocol involved a surgical technique and adjunctive treatment for specific cases. The adjunctive therapies used were intralesional steroids and calcitonin intranasal spray.

Surgical technique

The surgical technique was mucoperiosteal flap with incision placed 1cm further from radiographic extent of the lesion under 2% lidocaine with 1:80, 000 adrenaline infiltration. Buccal bone overlying lesion removed, enucleation and curettage of lesion performed. Teeth in area of lesion can be preserved if they are of good prognosis. Debridement of bony cavity and control of haemorrhage. The mucoperiosteal flap is repositioned, sutured and the sample sent for histology.

Adjunctive therapy

The protocol for intralesional steroid was a 50/50 mixture of 1 ml of 40 mg triamcinolone with 1 ml of 2% lidocaine with 1: 100, 000 adrenaline injected into the lesion once a week for six weeks and monitored radiographically. Our treatment modality for calcitonin intranasal spray was 200 iu (international units) per inhalation. Calcitonin intranasal spray was used as it is easy to administer.

Data collection

Data was collected on patient characteristics including sex, age at presentation, past medical history with blood test such as alkaline phosphatase, calcium, parathyroid hormone, and phosphate. The other features recorded ephrase s are missinge study arstification of the study areeatment modalities wchich is the main subject in the title.included anatomic site (mandible or maxilla), lesion size, treatment

modality (surgery or surgery with pharmacological therapy), recurrence, and time to recurrence. Data retrieved was stored and analysed using IBM SPSS statistics for windows Version 24. A correlation between categorical variables such as sex (male, female), site (maxilla, mandible), bone lesions, gingiva lesions and recurrence were tested using Fischer's exact test and results were presented as simple frequencies and descriptive statistics.

Results

Twenty-five histologically diagnosed giant cell granulomas were treated during a 12-year period. In our study, 9 patients (36%) were females, and 16 patients (64%) were males. More than 16 of the patients (64%) were aged 40 years and older. The age of our patients at presentation ranges from 7 to 76 years with an average age of 44.8. In our study they were more common in the maxilla 17 patient (68%) than mandible 8 patients (32%). Of this, 16 were peripheral giant cell while 9 were central giant cell granulomas (Table 1).

Age range	Frequency of Giant cell granulomas	%
0-10	4	16
11-20	1	4
21-30	3	12
31-40	1	4
41-50	3	12
51-60	5	20
61-70	4	16
71-80	4	16
Total	25	100

Table 1: *Distribution of giant cell granuloma according to age.*

Mean age/SD= 44.8 ± 22.65.

Blood tests analysed included serum calcium, alkaline phosphatase, parathyroid hormone, and phosphate levels. Alkaline phosphatase was increased in four of our patients with values ranging from 323 iu/L to 724 iu/L (normal levels 210-500 iu/L). Serum calcium values were reduced in two patients 2.15 and 2.18 mmol/L (normal levels 2.20 - 2.60 mmol/L) and a reduced phosphate level of 0.76 mmol/L (normal levels 0.9 - 1.8 mmol/L) in one patient. However, two patients had an elevated parathyroid level of 7.8 and 9.7 pmol/L (normal range 1.5 - 7.6 pmol/L), respectively (Table 2).

Case	Age	Sex	Site	Histology	Size in mm	Bloods	Recurrence
1	62	M	Mandible	PGC	38X16X9	PTH=9.7	N
2	24	M	Mandible	CGC	30X22X20	Normal	N
3	29	F	Maxilla	PGC	20X20X10	Normal	N
4	66	F	Mandible	CGC	60X50X30	ALK=323	N
5	72	M	Maxilla	PGC	12X10X5	Normal	N
6	71	M	Maxilla	CGC	10X7X3	Normal	Y 10 months
7	12	M	Maxilla	PGC	25X20X20	Pho=0.76	Y 16 months
8	49	M	Maxilla	PGC	16X7X6	Normal	Y 4 months
9	52	F	Mandible	CGC	24X12X7	Normal	Y4 months
10	76	M	Maxilla	CGC	15X8X6	Ca=2.15	Y 6 months

11	60	F	Mandible	CGC	7X5X4	Normal	N
12	26	F	Maxilla	PGC	6X5X5	N/A	N
13	60	M	Maxilla	PGC	15X10X7	Normal	N
14	8	M	Mandible	CGC	16X12X6	ALK=720	N
15	45	M	Maxilla	PGC	7X5X3	PTH=7.8	N
16	34	F	Maxilla	PGC	4X3X3	N/A	N
17	64	M	Maxilla	CGC	10X8X4	Normal	N
18	57	F	Mandible	PGC	7X4X3	Ca=2.18	N
19	7	M	Maxilla	PGC	60X45X30	Normal	N
20	61	M	Mandible	PGC	9X8X3	Normal	N
21	71	M	Maxilla	PGC	25X25X10	Normal	N
22	43	M	Maxilla	PGC	20X15X15	Normal	N
23	9	F	Maxilla	PGC	20X12X5	ALK=724	N
24	9	M	Maxilla	PGC	45X35X10	ALK=605	N
25	52	F	Maxilla	CGC	10X6X5	Normal	N

Table 2: *Demography of patients, site, size, and recurrence.*

M=Male; F=Female; CGC= Central Giant Cell Granuloma; PGC= Peripheral Giant Cell Granuloma; Y=Yes; N=No; PTH= Parathyroid Hormone; ALK=Alkaline Phosphatase; Ca= Calcium Pho= Phosphate; N/A=Not Available, Time to recurrence in months.

Twenty-three (92%) cases were managed with enucleation and curettage alone while two patients required surgical and adjunctive therapy. The adjunctive therapies used were intralesional steroid and calcitonin nasal spray. Recurrence rate was 20% (5 patients). In 3 patients we achieved clearance margin of 5 mm with further curettage and 2 patients had adjunctive therapy. The correlation between categorical variables such as sex, site (maxilla, mandible), bone lesions, gingiva lesions and recurrence were tested using Fischer's test with a value of 0.6206, 0.6416 and 0.6232. The results were statistically not significant and $p > 0.05$ (Table 3).

Categorical Variable	Recurrence	No recurrence	Fischer's test	P value
Male	4	12	0.6206	> 0.05
Female	1	8	0.6202	> 0.05
Maxilla	4	13	0.6416	> 0.05
Mandible	1	7	0.6416	> 0.05
Age over 40	4	12	0.6206	> 0.05
Age under 40	1	8	0.6206	> 0.05
Bone lesion	3	8	0.6232	> 0.05
Gingiva lesion	2	12	0.6232	> 0.05

Table 3: *Correlation between categorical variables.*

Discussion

The aim of our study was to present the treatment options of peripheral and central giant cell granulomas. To respond to the question, we report 25 cases treated at The Leeds Teaching Hospitals NHS Trust who had enucleation and curettage and pharmacological therapy

in cases of recurrence in addition to surgery. Giant cell granulomas can be classified as central or peripheral giant cell granulomas [13]. Also, the lesions can be aggressive and non-aggressive types based on clinical signs and pathological features. Aggressive behaviour as defined by Chuong., *et al*. 1986 and modified by Kaban., *et al*. 2002 include features such as size greater than 5 cm, pain, recurrence after curettage, rapid growth, paraesthesia, tooth displacement, root resorption, and cortical bone perforation [12,14].

In our study giant cell granuloma occur as a solitary lesion, presenting on panoramic radiographs as an area of unilocular radiolucency (Figure 1). The features seen on Cone Beam CT was a multilocular radiolucent lesion with well-defined borders, root resorption, cortical bone expansion and scalloped margins (Figure 2) [15]. In 14 (56%) of our patients, giant cell granulomas occur exclusively on gingiva and present as a reddish-blue nodular mass sessile or pedunculated which can be caused by local irritation and trauma (Figure 3 and 4). A total of 11 (44%) patients presented with bony involvement. There were 2 patients (8%) with recurrence of gingival lesions while 3 patients (12%) had bony lesions with recurrence.

Figure 1: *Cone beam CT right maxilla showing unilocular radiolucent lesion.*

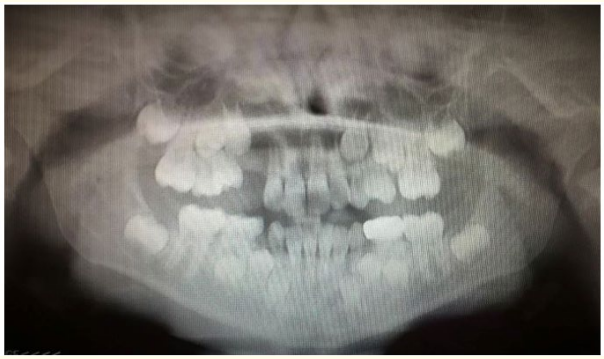

Figure 2: *Orthopantomogram.*

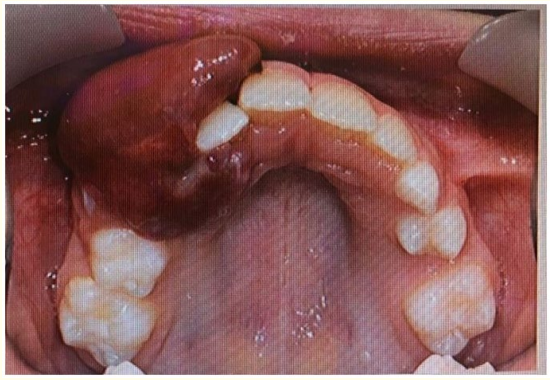

Figure 3: *Clinical photo palatal view of giant cell granuloma right maxilla.*

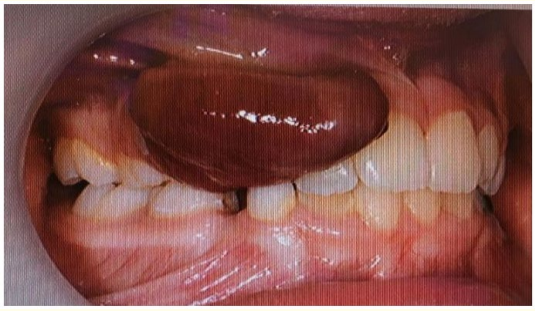

Figure 4: *Buccal view giant cell granuloma right maxilla.*

Our typical presentation of giant cell granulomas vary from small, asymptomatic, indolent, slowly growing lesions that are accidental findings on radiographs, to large lesions with cortical expansion, thinning and perforation, resorption of root, extending to adjacent margins as well as teeth, with associated pain and a tendency to recur after surgical treatment [1,13,15]. These lesions are encapsulated though can expands, pushing away and displacing adjacent structures [15,16]. Five patients (20%) presented with cortical bone perforation, four patients (16%) had lesions extension to adjacent tissue margins but there was no evidence of perineural invasion and displacement of adjacent structures.

Various treatments have been suggested for giant cell granulomas of the jaw bones. At The Leeds Teaching Hospitals NHS Trust, we have a good response to enucleation and curettage with a success rate of 92% [23 out of 25]. The surgical technique involved mucoperiosteal flap with enucleation and curettage. Surgical sample sent for histology reveals multi-nucleated giant cell with fibrovascular connective tissue stroma comprising areas of haemosiderin deposit surrounded by round, oval, spindle-shaped mononuclear cells (Figure 5). Post-operative review of the patient shows good healing (Figure 6 and 7).

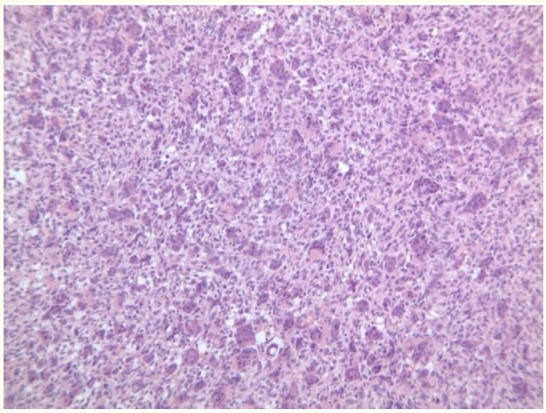

Figure 5: *Histology showing multinucleated giant cells.*

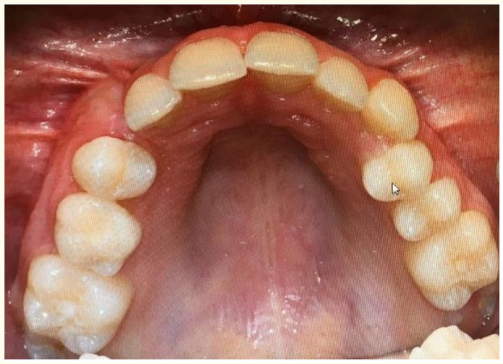

Figure 6: *Post-operative clinical photo of patient shows good healing.*

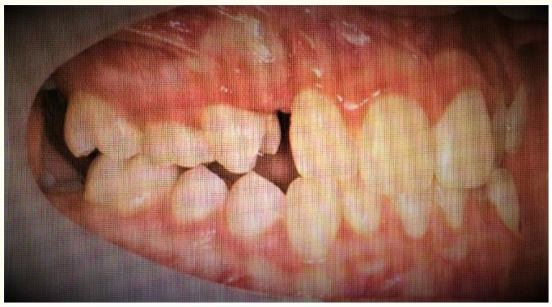

Figure 7: *Post-operative clinical photo buccal view.*

In our study the conventional treatment we used for giant cell granulomas was surgical intervention however because of the reported main shortcoming of surgery is a high recurrence rate [14,17], pharmacological agents were used as adjunctive treatment for two cases. The pharmacological adjunctive therapy resulted in 100% success rate though this was in 2 patients who had previous surgical intervention.

Pharmacological agents have been shown to be encouraging alternatives to surgical management. Proponents of these alternative treatment options state that pharmacological therapy has the potential to reduce recurrence rates while also minimizing surgical morbidity or even avoiding the need for surgical intervention [1,17].

Adjunctive therapies used for two of our cases include intralesional steroid injection. Intralesional steroid was first demonstrated by Jacoway in 1988 [17]. The protocol that was recommended is a 50/50 mixture of 2% lidocaine with 1: 100, 000 epinephrine with triamcinolone (Kenalog) and inject 2 mls per 1 cm of lesion as noticed on a panoramic radiograph and this were repeated six times at weekly intervals to suppress the inflammatory component of the lesion. This was used as an adjunctive therapy for one of our cases after recurrence.

Calcitonin has also been used as an adjunctive treatment for giant cell granulomas. It can be used via subcutaneous injection or intra-nasal spray, and it is generally well tolerated. It is a protein which decrease serum calcium concentration and inhibit osteoclastic activities in bone [18]. In our study, calcitonin intra-nasal spray was used as adjunctive treatment after enucleation and curettage. Calcitonin use was first demonstrated by Professor Malcom Harris in 1993. As central giant cell granulomas cannot be distinguished from brown tumour of hyperparathyroidism by histology alone, he proposed that there may be a parathyroid hormone-like hormone that could be the aetiology of this lesion [3,19]. The use of calcitonin in this patient was to inhibit the actions of parathyroid hormone. The technique used in our treatment was intra-nasal calcitonin as it was easy to deliver to the patient and the lesion was monitored radiographically [20]. There was a decrease in the tumour size, but this was used in one case with evidence of recurrence after enucleation and curettage.

Also, subcutaneous alpha interferon was reported in literature as adjunctive therapy. This assumed that giant cell granulomas may be vascular in origin. It was given because of its anti-angiogenic effects however there is insufficient evidence that the lesion is vascular in origin [3,21]. Some other studies suggested marginal mandibulectomy [22] with curettage and reconstruction with submental island flap is associated with less chances of recurrence however, using this treatment protocol may result in morbidity and longer hospital stay with a secondary procedure for bone graft and further reconstructive surgery [23]. This was not needed in any of the 25 cases treated at The Leeds Teaching Hospitals NHS Trust.

In our study, 16 patients [64%] presented at age 40 years and over with an average age of 44.8 years while 16 [64%] of the 25 patients were male. This was at variance to most studies [7,14,22,23] which reported a female preponderance (2:1) and patient presentation in the first three decades of life. This could be due to the epidemiological characteristics of our study population. Chrcanovic., *et al*. [24] presented 2270 cases review with around 60% of the patients were 9 - 41 year-old-women, with bone expansion in 92% of the cases, clinical symptoms in 21% of the cases, cortical bone perforation in 51%, and multiloculation with tooth displacement in 39%. Five [20%] of our patients presented with radiolucency, five [20%] with cortical bone perforation, two [8%] with root resorption, five [20%] with bone expansion and four [16%] with lesions extending to adjacent tissue margins. This is lower than the study conducted by Chrcanovic., *et al*. but this may be due to the smaller sample size and multiple publications were involved in Chrcanovic., *et al*. study.

In Chrcanovic., *et al*. study 365 scientific papers were reviewed comprising 2270 lesions, a recurrence was noted in 232 of 1316 cases (17.6%) and this is similar to the recurrence rate in our study (20%). However other studies have reported recurrence rate of 10 - 50%. Cortical bone perforation occurred in 50% of these cases. Marginal resection has been performed in aggressive and larger lesions and pharmacological therapy was more often in small lesions. However marginal resection was not needed in any of our patients nevertheless two of our patients with a lesion of 60 mm was treated with enucleation and curettage [1,13,22,24,25].

Some of the reported clinical features that predispose to greater rates of recurrence are root resorption, tooth displacement, and curettage as treatment [24,26]. In our study, four of the recurrences were in the maxilla and one in mandible. Of note is that recurrence was seen after extraction in two of the cases while the third was related to unerupted upper right canine. The fourth case of recurrence was seen after a repeat biopsy around upper right second premolar and first molar region while that in the mandible was related to extraction of the LR8 which had a further curettage of the socket to ensure clearance. There were two patients with giant cell granulomas on gingiva with recurrence and three with bony recurrence emerging from the socket. Also, the time to recurrence varied from 4 to 16 months**.** The sizes of the lesions in the five patients with recurrence were between 10 mm to 30 mm with a mean of 17 mm.

Factors like age, lesion size, gender, location, clinical symptoms, bone erosion does not influence the probability of recurrence. Our results are comparable to the published literature. Also, big lesions did not have recurrence. We examined gender, age, site, peripheral or central nature of lesion, and no statistical significant difference was identified.

The differential diagnosis that ought to be considered in the treatment of giant cell granuloma of the jaw bones include Odontogenic keratocyst, Odontogenic myxoma, Multicentric giant cell tumours of bone, Pyogenic granuloma, Brown tumour of hyperparathyroidism, Cherubism, Aneurysmal bone cyst, Ossifying fibroma, Neurofibromatosis and Noonan syndrome (Table 4).

Reactive Lesions
- Primary Hyperparathyroidism
- Noonan syndrome
Tumours of the bone:
- Giant cell tumours (Osteoclastoma)
- Idiopathic histiocytosis
• Letterer-Siwe disease
• Hand-Schuller Christian disease
• Eosinophilic granuloma
- Paget's disease of bone
Connective tissue hyperplasia
- Pyogenic granuloma
Non- epithelialized primary bone cyst
- Aneurysmal bone cyst
- Solitary bone cyst
- Traumatic bone cyst
Fibro-osseous lesions
- Fibrous dysplasia
- Ossifying fibroma
- Cemento-osseous dysplasia
- Cherubism
Cystic lesions
- Odontogenic keratocyst
- Odontogenic Myxoma
Genetic
- Neurofibromatosis
- Gorlin-Goltz syndrome

Table 4: *Differential diagnosis of giant cell granulomas of the jaws.*

In the treatment of giant cell granulomas of the jaws, incisional biopsy is necessary for the diagnosis and further tests including serum plasma calcium, parathyroid hormone, phosphate, and alkaline phosphatase to exclude Brown tumour of hyperparathyroidism. Of importance was that at least 23 of our patients had bloods and there were nine patients with abnormal blood results with four patients having elevated alkaline phosphatase, two with elevated parathyroid hormone levels, two with reduce calcium level and one with reduced phosphate levels. Brown tumour of hyperparathyroidism was ruled out as none of our patients had both an increase in calcium and parathyroid level. Afterwards all the blood parameters were tested a few months afterwards and were all normal.

Conclusion

Our study emphasizes the role of surgery in the treatment of peripheral and central giant cell granulomas and the use of adjunctive pharmacological agents in cases of recurrence. As there is a lack of consensus in the treatment of giant cell granulomas in current literature, we recommend surgical treatment as first line of treatment and pharmacological agents like intralesional steroid or calcitonin as adjunctive therapy. Also, there is a need to develop an international standard on the management of giant cell granulomas of the jaws. To summarize the findings of our study we had a good response to enucleation and curettage of the lesion independent of initial presentation and behaviour of the tumour with a recurrence rate of 20%. In those with recurrence we have achieved clearance with further curettage and use of adjunctive therapy in two patients.

Conflict of Interest

None.

Acknowledgement

An abbreviated presentation of the results of this study was delivered at the British Association of Oral Surgeons (BAOS) Scientific Conference in March 2024.

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