Int. J. Oral Maxillofac. Surg. 2016; 45: 756–759
http://dx.doi.org/10.1016/j.ijom.2016.02.016, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper

Clinical Pathology

Can calcitonin nasal spray reduce the risk of recurrence of central giant cell granuloma of the jaws? A double-blind clinical trial

R. Tabrizi[1], S. Fardisi[2], B. Zamiri[1], S. Amanpour[2,3], T. Karagah[1]

[1]Department of Oral and Maxillofacial Surgery, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Department of Oral and Maxillofacial Surgery, School of Dentistry, Kerman University of Medical Sciences, Kerman, Iran; [3]Oral and Dental Diseases Research Centre, Kerman University of Medical Sciences, Kerman, Iran

R. Tabrizi, S. Fardisi, B. Zamiri, S. Amanpour, T. Karagah: Can calcitonin nasal spray reduce the risk of recurrence of central giant cell granuloma of the jaws? A double-blind clinical trial. Int. J. Oral Maxillofac. Surg. 2016; 45: 756–759.

Abstract. Recurrence is a major problem following the treatment of aggressive central giant cell granuloma (CGCG). The aim of this study was to compare the frequency of recurrence between patients who received calcitonin nasal spray after curettage of CGCGs and those who did not. A double-blind clinical trial was designed. Patients were allocated to one of two groups: those in the calcitonin group underwent curettage and received calcitonin salmon nasal spray 200 IU/day once a day for 3 months after surgery; those in the control group underwent curettage of CGCGs and received a placebo once a day for 3 months after surgery. All patients were followed for 5 years after surgery. Twenty-four patients were treated in the two groups. There was no difference in age, sex, tumour size, or tumour location between the two groups ($P > 0.05$). Eight of the 24 patients (33.3%) had recurrences during the follow-up period: one in the calcitonin group (9.1%) and seven in the control group (53.8%). Analysis of the data demonstrated a significant difference between the two study groups ($P = 0.033$). It appears that calcitonin nasal spray may reduce the frequency of recurrence in aggressive CGCGs in the mandible and maxilla.

Key words: central giant cell granuloma; recurrence; calcitonin; maxilla; mandible.

Accepted for publication 29 February 2016
Available online 15 March 2016

Central giant cell granuloma (CGCG) is a benign lesion of the jawbones. The incidence of CGCG is about 0.00011% of the general population.[1] CGCGs have variable behaviours and clinical presentations, ranging from large lesions with aggressive behaviour to small isolated lesions.[2] The clinical signs and symptoms and the radiographic and histological features are the main factors differentiating non-aggressive (indolent) from more aggressive lesions.[3] Lesions larger than 5 cm and/or recurrent lesions are considered aggressive lesions based on clinical characteristics. The non-aggressive lesions

are asymptomatic with no radiographically visible cortical perforation or root resorption.[4]

Local curettage is the conventional treatment for CGCGs. En bloc resection has been suggested for aggressive CGCGs. The recurrence rate following local curettage in aggressive CGCGs is between 16% and 48%.[5] En bloc resection is associated with the lowest recurrence rate.[6] However, en bloc resection results in various degrees of deformity and requires complex reconstruction procedures.[3]

In the past two decades, various pharmacological therapies for CGCGs have been described.[7] Pharmacological agents prevent or at least minimize the extensive and mutilating surgical procedures characterized by detrimental functional outcomes and preserve vital structures and facial contours.[7] Pharmacological agents that have been used successfully include intra-lesional corticosteroid injections and systemic treatment with calcitonin or interferon alpha-2a (IFN-α2a).[7,8] Harris introduced calcitonin therapy for CGCGs.[9] The mode of action of calcitonin in the treatment of CGCGs is antagonistic osteoclastic bone resorption, or direct action on other cell types within the lesion.[10] Calcitonin has been considered a viable option for the treatment of CGCGs. It is suggested for multiple lesions, recurrent lesions, and aggressive lesions.[10]

In studies reported in the literature, calcitonin has been applied for the treatment of CGCGs either alone or as an adjunct agent.[11] However, it has not been used to prevent recurrence in the management of CGCGs. Thus, this study was performed to assess the use of calcitonin after curettage of aggressive CGCGs to determine whether it reduces the frequency of recurrence or not. It was hypothesized that calcitonin would decrease recurrence after conventional curettage of CGCGs of the jaws.

Materials and methods

A double-blind randomized clinical trial was designed. The sample was derived from the population of patients referred to the oral and maxillofacial surgery department of a medical university in Shiraz, Iran, between 1 September 2006 and 31 October 2010. The study was approved by the necessary medical ethics committee and has been registered at ClinicalTrials.gov (registration ID NCT02358304).

Subjects eligible for inclusion had a clinically aggressive CGCG and underwent curettage. All subjects had computed tomography (CT) scans taken before surgery. Participants with a systemic disease affecting bone healing, a brown tumour proven by laboratory test (parathyroid hormone, calcium phosphatase), pregnancy, recent corticosteroid therapy, and those who refused enrolment or could not continue for private or social reasons, were excluded from the study.

The diagnosis of CGCG was made initially by histopathological examination. Aggressive CGCGs were defined as lesions with a diameter >5 cm on CT scan views, with perforation of the buccal and lingual plates or root resorption.

Thirty patients were allocated randomly to two groups. Patients in the calcitonin group ($n = 15$) underwent curettage of CGCGs and received calcitonin salmon nasal spray 200 IU/day once a day for 3 months after the surgery. Patients in the control group ($n = 15$) underwent curettage of CGCGs and received a placebo once a day for 3 months after surgery. Patients were followed by a maxillofacial surgeon who did not participate in the surgeries and was blinded to the group allocation of subjects. Furthermore, none of these surgeons was aware of the research. Patients were blinded to the type of drugs they had received after surgery.

All patients were followed up for 5 years after the operations. Cases of recurrence were documented by clinical and radiographic examinations and confirmed by histopathological analysis.

Age, sex, location (maxilla or mandible), and tumour size were considered as variables. Calcitonin was the predictive factor of the study. Recurrence of the CGCGs determined the outcome of the study.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). A pre-protocol analysis was conducted. The Shapiro–Wilk test was used to document normally distributed age of the samples. The independent *t*-test was applied to compare age and tumour size between the groups (treatment group with calcitonin and control group). Fisher's exact test was applied to assess the frequency of recurrence and variables (tumour location and sex) between the two groups.

Results

A final total of 24 patients were studied in the two groups: 11 in the calcitonin group and 13 in the control group. Six of the initial 30 patients dropped out at random; these patients did not follow the study protocol, or failed to complete the follow-up. The calcitonin group (treatment group) comprised five males and six females and the control group comprised six males and seven females. There was no difference between the two groups in sex distribution ($P = 0.64$). The mean patient age was 24.36 ± 4.29 years in the calcitonin group and 24.61 ± 4.64 years in the control group. Comparison of the mean age between the groups did not show a statistically significant difference ($P = 0.83$) (Table 1).

The mean tumour size was 6.40 ± 0.88 cm in the calcitonin group and 6.26 ± 0.97 cm in the control group. Evaluation of tumour size did not demonstrate a significant difference between the groups ($P = 0.71$). In the calcitonin group, seven patients had CGCGs in the maxilla and four had CGCGs in the mandible. In the control group, seven patients had CGCGs in the maxilla and six had CGCGs in the mandible. There was no statistically significant difference in tumour location (maxilla or mandible) between the groups ($P = 0.47$) (Table 1).

The mean time to recurrence was 23.5 ± 8.75 months (Table 2). Eight of 24 patients (33.3%) had a recurrence. One patient (9.1%) in the calcitonin group

Table 1. Comparison of variables between the two groups.

Variables	Group 1 Calcitonin group	Group 2 Control group	*P*-value
Tumour location			0.47[a]
Mandible	4	6	
Maxilla	7	7	
Sex			0.64[a]
Male	5	6	
Female	6	7	
Tumour size, mean ± SD (cm)	6.40 ± 0.88	6.26 ± 0.97	0.71[b]
Age, mean ± SD (years)	24.36 ± 4.29	24.61 ± 4.64	0.83[b]

SD, standard deviation.
[a] Fisher's exact test.
[b] Independent *t*-test.

Table 2. Description of the patients with recurrence.

Recurrence case	Group	Sex	Age (years)	Site	Time of recurrence (months)	Tumour size (cm)
1	1	Female	24	Maxilla	33	8
2	2	Female	29	Maxilla	27	7
3	2	Male	19	Maxilla	18	8
4	2	Male	28	Maxilla	26	7
5	2	Female	18	Maxilla	10	7
6	2	Male	26	Maxilla	22	6
7	2	Male	25	Maxilla	36	6
8	2	Female	22	Maxilla	16	7

Table 3. Evaluation of the recurrence rate (study outcome) between the two groups.

Outcome	Group 1 Calcitonin group	Group 2 Control group	Fisher's exact test
Recurrent lesion	1	7	$P = 0.033$
No recurrence	10	6	

and seven patients (53.8%) in the control group had a recurrence during the 5-year follow-up. Analysis of the data demonstrated a significant difference between the two groups in this regard ($P = 0.033$) (Table 3). All patients with recurrence underwent en bloc resection. None of the patients with a resected lesion had a secondary recurrence.

The variables age, sex, tumour location, and tumour size were compared between patients with and without recurrence irrespective of calcitonin use. Eight of 14 patients (57.1%) with CGCGs in the maxilla had a recurrence. None of the patients with mandibular lesions had a recurrence. There was a significant difference in recurrence between the mandible and maxilla ($P = 0.006$). Results did not reveal a significant difference for age or sex between patients with and without recurrence ($P > 0.05$). There was a significant difference in tumour size between the recurrence group and the group without recurrence ($P = 0.003$) (Table 4).

Discussion

In cases of aggressive CGCG, extensive surgical procedures resulting in functional and aesthetic deformities and the high recurrence rate following conventional curettage have prompted surgeons to seek an effective therapeutic strategy. Giant cells may arise from peripheral blood mononuclear cells that are recruited by the spindle-shaped stromal cells.[2] These spindle-shaped cells are osteoblast-like cells that express alkaline phosphatase and are capable of osteoid formation. They are also able to support osteoclast formation and cause tumour-like lesions.[2]

The treatment of CGCGs includes conservative surgical procedures and pharmacological agents such as local corticosteroids, IFN-α, and calcitonin injections. Lesions are considered aggressive CGCG if they are larger than 5 cm in diameter, show rapid growth, cause tooth displacement, root resorption, cortical bone thinning, or perforation, and have a high recurrence rate (20–70%). En bloc resection has been recommended for such cases.[12] At present, there are other (non) surgical options that should be considered as the first-line treatment for an aggressive CGCG.

Histological, biochemical, molecular, or genetic markers should not be considered as predictive factors for the biological behaviour of CGCG lesions. Pharmacological agents have usually been used to prevent or minimize extensive surgical procedures.[12] Calcitonin is a polypeptide hormone made up of 32 amino acids, and is secreted by the parafollicular thyroid C-cells. It decreases circulating levels of calcium via the inhibition of the activity of osteoclasts; this, in turn, destroys mineralized bones. In jaw lesions, calcitonin inhibits their growth via the effects mediated by the calcitonin receptor (CTR).[11] Giant cells have been shown to express osteoclastic markers, such as tartrate-resistant acid phosphatase (TRAP), vitronectin, and CTR, and can resorb lacunar bone *in vitro*.[13] Aggressive CGCGs have higher CTR expression. Also, Nogueira et al. reported no significant difference in CTR expression in the different clinical forms of CGCGs.[14]

Calcitonin is used as an adjunct for the treatment of CGCGs. Calcitonin has been shown to reduce the size of CGCG lesions while increasing the calcification and thickening of the cortical Plates.[15] Significant, stable clinical and radiographic bone remodelling has been reported after 1 year of calcitonin treatment of CGCG.[12] The recommended daily dose of calcitonin as a nasal spray is 200 IU.[12] The nasal spray has the advantage of avoiding daily injections, and the side effects are considerably less in comparison with subcutaneous injections.[16] However, the disadvantages of nasal spray include the low absorption of calcitonin through the nasal mucosa, which is variable and ranges between 20% and 100% when compared to injections.[10] Thus, a daily dose of 400 IU calcitonin nasal spray would be equivalent to as low as 80 IU and as high as 400 IU of the injected calcitonin.[12] In the present study, a low dose of nasal calcitonin was used (200 IU).

All previous studies have used calcitonin alone or in conjunction with other pharmacological agents for the treatment of CGCGs.[2,3,14] In reviewing the literature, no document regarding the use of calcitonin for the prevention of recurrence after surgical interventions was identified. de Lange et al. studied calcitonin therapy in CGCG of the jaw in 14 patients[2]; complete remission was not observed. They reported that changes in tumour size were variable in patients with aggressive lesions, whereas a decrease or stabilization of the tumour size occurred for indolent lesions.[2] The use of calcitonin has been suggested as a supplementary treatment for aggressive CGCGs.[17] The present research showed a significant reduction in the frequency

Table 4. Effect of variables on the frequency of recurrence, irrespective of the use of calcitonin.

Variables	With recurrence	Without recurrence	*P*-value
Tumour location			0.006[a]
Mandible	0	10	
Maxilla	8	6	
Sex			0.55[a]
Male	4	7	
Female	4	9	
Tumour size, mean ± SD (cm)	5.97 ± 0.76	7.06 ± 0.78	0.003[b]
Age, mean ± SD (years)	23.87 ± 3.97	24.81 ± 4.67	0.51[b]

[a] Fisher's exact test.
[b] Independent *t*-test.

of recurrence in the group treated with calcitonin after surgery. It could be hypothesized that the remaining CGCG lesions after curettage are suppressed through the CTR.

The re-proliferation of giant cells could be affected by calcitonin. The administration of calcitonin has been shown to result in CTR-mediated alterations in cell structure and subsequent inhibition of DNA synthesis by the cells.[18] Two distinct cDNAs encoding the CTRs on CGCGs have been reported.[19] It has been concluded that the first intracellular domain of the CTR is involved in ligand binding and signal transduction via the G protein/adenylate cyclase system.[18] Recent evidence may suggest an association between salmon calcitonin use and cancer incidence based on studies with poor-quality cancer assessment methods. This evidence may be considered as a limitation in the use of calcitonin.[20]

In this study, calcitonin was used for 3 months after surgery. Tanko et al. showed that 3 months of calcitonin therapy was effective in bone formation.[21] The use of calcitonin to reduce recurrence needs further study; for example, to determine whether longer administration of calcitonin enhances its prevention capacity or not (or if an increased dose of calcitonin affects clinical results). An examination of CTR was not performed in this study, which could be considered a limitation.

In conclusion, it appears that calcitonin nasal spray may reduce the frequency of recurrence of aggressive CGCGs in the mandible and maxilla.

Funding

The authors thank the Vice Chancellor of Shiraz University of Medical Sciences for supporting this research (grant 91-01-03-5278). This manuscript is based on a thesis by Dr Sorena Fardisi.

Competing interests

No conflict of interest.

Ethical approval

This study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences.

Patient consent

All subjects provided signed consent to participate in the study.

References

1. de Lange J, van den Akker HP, Klip H. Incidence and disease-free survival after surgical therapy of central giant cell granulomas of the jaw in The Netherlands: 1990–1995. *Head Neck* 2004;**26**:792–5.
2. de Lange J, van den Akker HP, Veldhuijzen van Zanten GO, Engelshove HA, van den Berg H, Klip H. Calcitonin therapy in central giant cell granuloma of the jaw: a randomized double-blind placebo-controlled study. *Int J Oral Maxillofac Surg* 2006;**35**:791–5.
3. Rachmiel A, Emodi O, Sabo E, Aizenbud D, Peled M. Combined treatment of aggressive central giant cell granuloma in the lower jaw. *J Craniomaxillofac Surg* 2012;**40**:292–7.
4. Schmidt B. *Benign nonodontogenic tumors in oral and maxillofacial surgery.* Saunders-Elsevier; 2009: 592–610.
5. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws: a clinical, radiologic, and histopathologic study. *Oral Surg Oral Med Oral Pathol* 1993;**75**:199–208.
6. Shirani G, Abbasi AJ, Mohebbi SZ, Shirinbak I. Management of a locally invasive central giant cell granuloma (CGCG) of mandible: report of an extraordinary large case. *J Craniomaxillofac Surg* 2011;**39**:530–3.
7. Schreuder WH, Coumou AW, Kessler PA, de Lange J. Alternative pharmacologic therapy for aggressive central giant cell granuloma: denosumab. *J Oral Maxillofac Surg* 2014;**72**:1301–9.
8. Kaban LB, Troulis MJ, Wilkinson MS, Ebb D, Dodson TB. Adjuvant antiangiogenic therapy for giant cell tumors of the jaws. *J Oral Maxillofac Surg* 2007;**65**:2018–24.
9. Harris M. Central giant cell granulomas of the jaws regress with calcitonin therapy. *Br J Oral Maxillofac Surg* 1993;**31**:89–94.
10. Pogrel M. Calcitonin therapy for central giant cell granuloma. *J Oral Maxillofac Surg* 2003;**61**:649–53.
11. Borges HO, Machado RA, Vidor MM, Beltrão RG, Heitz C, Filho MS. Calcitonin: a non-invasive giant cells therapy. *Int J Pediatr Otorhinolaryngol* 2008;**72**:959–63.
12. Vered M, Shohat I, Buchner A, Dayan D, Taicher S. Calcitonin nasal spray for treatment of central giant cell granuloma: clinical, radiological, and histological findings and immunohistochemical expression of calcitonin and glucocorticoid receptors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**104**:226–39.
13. Vered M, Buchner A, Dayan D. Immunohistochemical expression of glucocorticoid and calcitonin receptors as a tool for selecting therapeutic approach in central giant cell granuloma of the jawbones. *Int J Oral Maxillofac Surg* 2006;**35**:756–60.
14. Nogueira RL, Faria MH, Osterne RL, Cavalcante RB, Ribeiro RA, Rabenhorst SH. Glucocorticoid and calcitonin receptor expression in central giant cell lesions: implications for therapy. *Int J Oral Maxillofac Surg* 2012;**41**:994–1000.
15. Sadiq Z, Goodger N. Calcitonin-induced osteoplastic reaction in the mandible. *Br J Oral Maxillofac Surg* 2011;**49**:578–9.
16. de Lange J, Rosenberg AJ, van den Akker HP, Koole R, Wirds JJ, van den Berg H. Treatment of central giant cell granuloma of the jaw with calcitonin. *Int J Oral Maxillofac Surg* 1999;**28**:372–6.
17. Triantafillidou K, Venetis G, Karakinaris G, Iordanidis F. Central giant cell granuloma of the jaws: a clinical study of 17 cases and a review of the literature. *Ann Otol Rhinol Laryngol* 2011;**120**:167–74.
18. Allon DM, Anavi Y, Calderon S. Central giant cell lesion of the jaw: nonsurgical treatment with calcitonin nasal spray. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;**107**:811–8.
19. Gorn AH, Rudolph SM, Flannery MR, Morton CC, Weremowicz S, Wang TZ, et al. Expression of two human skeletal calcitonin receptor isoforms cloned from a giant cell tumor of bone. The first intracellular domain modulates ligand binding and signal transduction. *J Clin Invest* 1995;**95**:2680.
20. Overman RA, Borse M, Gourlay ML. Salmon calcitonin use and associated cancer risk. *Ann Pharmacother* 2013;**47**:1675–84.
21. Tankó LB, Bagger YZ, Alexandersen P, Devogelaer JP, Reginster JY, Chick R, et al. Safety and efficacy of a novel salmon calcitonin (sCT) technology-based oral formulation in healthy postmenopausal women: acute and 3-month effects on biomarkers of bone turnover. *J Bone Miner Res* 2004;**19**:1531–8.

Address:
Reza Tabrizi
OMFS Department
Shahid Beheshti Dental School
Velenjak
Tehran
Iran
Tel: +98 9125850829
E-mail: Tabmed@gmail.com