Effects of Salmon Calcitonin on Patients With Atypical (Idiopathic) Facial Pain: A Randomized Controlled Trial

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The analgesic properties of salmon calcitonin for the treatment of atypical facial pain (AFP) were investigated. An initial open-label trial of salmon calcitonin in subjects with refractory AFP was followed with a randomized, double-blind, placebo-controlled crossover trial of salmon calcitonin in the management of AFP. Salmon calcitonin (100 IU in 1 mL saline) was administered in an open-label fashion to 13 subjects with refractory AFP five times per week for 6 weeks. In the subsequent randomized investigation, salmon calcitonin (100 IU in 1 mL saline) or placebo (1 mL saline) was delivered three times per week for 3 weeks, with a 1-week washout prior to crossover. The percentage of subjects dropping out (57%) exceeded that reported in other pain studies using calcitonin. Therefore, it was imperative to halt the study for ethical reasons. There was no difference in outcome measures ($P > .05$) in subjects administered either active drug or placebo, and a high incidence of side effects led to dropout in subjects taking salmon calcitonin. Although salmon calcitonin may have analgesic properties, it is not efficacious for AFP, largely because of the side effects.

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Atypical facial pain (AFP) is characterized by severe chronic intractable pain. Although this condition has been well recognized in the literature,[1–5] its identification in clinical practice is not as obvious and is often based on exclusion rather than inclusion criteria.[6,7] In this regard, the diagnosis of AFP may be based on findings that essentially exclude the presence of other craniofacial pain conditions, even though it does have some characteristic features. For example, the pain associated with AFP is usually constant with fluctuations in intensity. In addition, the pain is most often unilateral and may tend to afflict the upper half of the face; however, it may not follow classic sensory nerve distributions.[1–5,8]

The etiology of AFP is unknown, but one of the most enduring hypotheses relates its cause to a psychogenic model. Numerous investigators correlated the presence of AFP with varying forms and degrees of psychopathologic processes including, notably, depression.[9,10] Unfortunately, few of the studies linking psychiatric disorders with AFP were prospective in their design. Thus, it is difficult to determine whether AFP may have provoked the development of the psychiatric illness or was generated by it. Others have suggested a more neurologic pathophysiology not unlike that related to deafferentation syndromes such as phantom

limb pain,[2,11] or vascular pain phenomena such as facial migraine.[2,4,7,11,12] Certainly, there are data that support various mechanisms for AFP and that suggest that this affliction comprises a heterogeneous group of pain disorders with similar pain presentations. Indeed, any or all of the aforementioned proposed mechanisms may play a role in any one patient, and the present study may explain why AFP is so difficult to treat. Because no clear cause for the pain has been determined, it may be suggested that the condition be named *idiopathic* facial pain rather than *atypical* facial pain.

Effective therapies for AFP are not likely to be developed without a greater understanding of its underlying pathophysiology. Nonetheless, there is a pressing need to develop more predictable and reliable treatment strategies for AFP. Undoubtedly, this is required for patient comfort, but there is also evidence to suggest that the presence of pain may modify neural processing and may perpetuate the painful state.[13] Although the mechanisms underlying AFP are not well understood, certain cases of AFP may be attributable to a deafferentation phenomenon not unlike phantom limb pain.[11] On this basis, it was hypothesized that some treatments that have demonstrated utility for phantom limb pain,[14,15] such as use of the osseotropic hormone, salmon calcitonin (SC), might also be useful for AFP. Notably, this hormone is used primarily for its effects on bone resorption, in that it inhibits osteoclast activity.[16] It has also been shown to reduce bone pain in patients with osteoporosis before changes in the skeleton can be expected; therefore, it may also have ancillary analgesic activity.

To test this hypothesis in the present study, an exploratory investigation was undertaken to determine whether SC could be used in the management of refractory (ie, nonresponsive to treatment) AFP. Some patients with AFP in this open-label trial (ie, both patients and clinicians were aware that active drug was being administered) reported improvement when given SC. In addition, these patients reported a higher incidence of side effects than was expected on the basis of the manufacturer's monograph or previous investigations. Because the patients treated in the open-label trial had not responded to previous interventions, the fact that any of these individuals reported a reduction in their pain ratings was considered promising. Furthermore, the incidence and severity of side effects was also striking, given previous data indicating that mild and transient effects could be expected. In view of these findings, a randomized, placebo-controlled, double-blind trial was carried out in the present study to determine the true effectiveness of SC and to confirm the incidence of side effects in the management of patients with refractory AFP.

Materials and Methods

Open-Label Treatment

Prior to embarking on a more rigorous investigation of the effects of SC on AFP, SC was administered to patients being treated for AFP at the Craniofacial Pain Research Unit, Mount Sinai Hospital, Toronto, Ontario, Canada, under open-label conditions. This was done on compassionate grounds because this particular group of patients had not responded to any previous treatment interventions or they suffered such severe side effects with antidepressant medications so as to preclude further treatment. Available studies[14,15] on the use of SC for treatment of pain indicated that side effects were minimal; therefore, SC was considered a potentially useful alternative medication, even in patients who had experienced previous intolerable side effects with other drugs. Salmon calcitonin (Miacalcic, Sandoz Pharmaceuticals, Laval, Quebec, Canada; lot number 269MFDO893) was administered in an open-label fashion to these patients (Table 1). Only patients who could not take SC for health reasons were denied the medication. A nurse at the patient's home administered 100 IU of SC subcutaneously on weekdays for 6 weeks. This dosage has been shown

Table 1 Patient Age, Gender, and Ability to Tolerate SC During Open-Label Conditions in the Pilot Study

Gender	Age	Able to tolerate SC
M	71	Y
F	43	Y
F	45	Y
F	35	Y
F	56	Y
F	31	Y
F	70	Y
F	30	Y
F	44	Y
F	43	N
F	43	N
F	65	N
F	40	N

previously to be effective against the pain of osteoporotic fractures. In these cases, pain relief was reported after either 100 IU/day[17] or 50 IU/day.[18] Although previous reports have shown that phantom limb pain was relieved 5 minutes after a single administration of 100 IU[14] or 200 IU[15] of SC, other pain conditions may require longer therapy to promote analgesia. Thus, a more prolonged course of treatment was chosen.

Because this was a novel approach to the management of AFP, some outcome measures were defined to monitor the patients' progress while on this medication. Patients were asked to complete a digital pain scale (DPS) prior to treatment and every week during the administration of the drug. The DPS consists of a horizontal line with circles to designate one-unit intervals between 0 and 10, and it was developed to aid in diagnosis and assessment of various facial pain conditions, including AFP.[8] Subjective reports of treatment response were solicited from patients to indicate whether they felt better, the same, or worse. For the purpose of data analysis responses denoting "better" were considered successful, and responses denoting "the same" or "worse pain" were deemed unsuccessful. Patients were also asked to report side effects on a weekly basis. Blood was sampled at the first (baseline) and last weeks. A complete blood count was done and levels of serum calcium, phosphate, and alkaline phosphatase were also measured because these parameters might be altered by SC. Similar outcome measures were used in the randomized controlled trial.

Randomized Controlled Trial

From findings obtained in the open-label pilot treatment, it became clear that a more objective test was required to demonstrate whether SC would be useful for management of AFP.

Subject Selection. For the randomized controlled trial, subjects who had not participated in the open-label trial were recruited from the Craniofacial Pain Research Unit at the Mount Sinai Hospital and through advertisements in newspapers. Prospective subjects were assessed with a detailed interview in the same manner as all patients seeking treatment at the Mount Sinai Hospital Craniofacial Pain Research Unit. Separate clinical examinations were performed by a dentist and a neurologist to determine the source of the pain. Additional investigations such as those with conventional radiographs and ^{99m}technetium bone scans were performed to rule out underlying disease when this was suggested on radiographs.

Subjects were accepted into the study if they conformed to specific inclusion criteria for AFP as described by Graff-Radford and Solberg[6] and Marbach[11] to ensure a homogeneous patient group. Subjects were included if they fulfilled the following requirements:

1. Dentoalveolar pain longer than 6 months.
2. Unilateral pain.
3. Constant pain. (Fluctuations in intensity were allowed.)
4. Absence of associated musculoskeletal/dental or organic disease.
5. Women between ages 20 and 60 years.
6. Negative findings on bone scan of the region.

Exclusion criteria were employed to avert confounding variables or untoward effects of SC in susceptible individuals and were as follows:

1. Any conditions for which the use of SC is contraindicated, including an allergy to fish or fish products, pregnancy, or lactation
2. A known history of metabolic bone disease; renal calculi; cardiac disease; abnormal levels of serum calcium, alkaline phosphatase, inorganic phosphate, or magnesium
3. Any significant systemic disease

It should be noted that similar diagnostic and exclusion criteria were used for the open-label trial, with some exceptions (eg, men were included in the open-label trial). Prior to entering the randomized study, subjects were given an information package, their questions were answered, and signed consent forms were obtained.

The pain experienced by subjects in the present study was generally described as being boring or pressurelike rather than aching or throbbing. Although preliminary data suggest that the pain in some subjects with AFP can be attenuated even with placebo anesthetic injections, in other subjects the pain may not be reduced following a full anesthetic nerve block on the affected side.[19] Thus, it may have been interesting to separate subjects on the basis of their response to local anesthetic. However, because these findings require further exploration and confirmation, such testing was not carried out on subjects in the present study.

Treatment Protocol for the Randomized Controlled Trial. Subjects were placed into one of two groups on the basis of a coin toss performed by a nurse who ensured that the double-blind protocol was upheld. Subjects in group 1 received inactive placebo injections for a period of 3 weeks (1 mL of saline per subcutaneous injection) followed by 1 week of washout and then

another 3 weeks of treatment with 100-IU subcutaneous injections of SC in 1 mL of saline. For group 2 subjects the order of treatment was reversed (SC, washout, placebo).

Because SC was being administered under study conditions, subjects had to present to the clinic to ensure uniformity of drug or placebo injections. Concern from the institutional ethics committee that five clinic visits per week was excessive led to protocol modification so that subjects had to present only three times a week. Consequently, during periods in which SC was given, subjects received a total dose of 300 IU/week. Similar regimens have been used in other studies[20] in which improvement in symptoms has been noted. In fact, the dose and treatment regimen used in the present study fell within dose ranges and administration schedules used in a number of investigations[14,15,18,20–23] that showed SC-mediated pain relief, and thus, it was considered appropriate. In some reports,[14,15] SC-mediated analgesia was observed almost immediately after administration of the drug. The washout was performed to ensure no carry-over effect, even though previous studies suggest that this may not occur.[21]

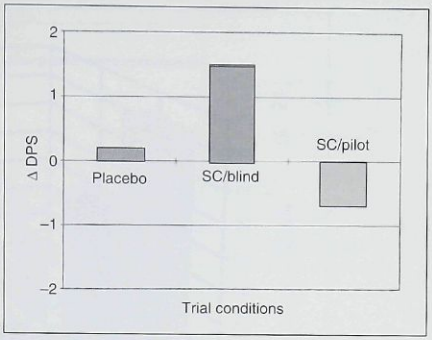

Fig 1 Change in DPS scores (DPS final – DPS initial = ΔDPS) after treatment with placebo or SC under either randomized controlled trials (SC/blind) or open-label (SC/pilot) conditions. There were insignificant increases in pain scores after 3 weeks of administration of either SC or placebo under double-blind conditions and a non-significant decrease in the pain scores after 6 weeks of SC treatment under open-label conditions. Note that a positive score denotes an increase in reported pain.

Results

Sample size calculations indicated that approximately 35 subjects would be required to obtain statistically significant results.[24] However, it became apparent that the expected incidence of side effects had been grossly underestimated. The majority of subjects reported side effects that were often so severe that they were forced to withdraw from the study. Therefore, it became clear that participants could not be assured, a priori, that the possibility of side effects was either negligible or manageable, and it was decided that the randomized controlled trial had to be terminated prematurely for ethical concerns, particularly in the face of what appeared to be no clinical benefit. The aforementioned notwithstanding, the data obtained from this limited sample is described here.

Open-Label Treatment

Thirteen patients suffering from AFP consented to receive SC for their pain under open-label conditions; all but one were women. Nine of the patients (69%) completed 6 weeks of SC treatment; four dropped out because of side effects. The initial DPS was subtracted from the final DPS to determine if SC treatment resulted in a net decrease in pain levels. In the nine patients who were able to tolerate 6 weeks of SC, there was a slight improvement in the mean DPS of 0.7 ($P > .05$, paired Student's t test) (Fig 1).

Subjective self-assessment of recovery showed that five of the nine patients reported that their pain was better on at least 50% of the reports; one patient noted that her pain was worse on at least 50% of the reports and the remaining three patients reported that their pain was the same on at least 50% of the reports. Four of the thirteen patients (31%) dropped out within the first week of treatment because of nausea and vomiting. Of the nine patients who completed 6 weeks of SC therapy, all reported a side effect at least one time (Fig 2). In total, for the patients who continued taking SC, there was a complaint of at least one side effect during 48% of the visits.

Randomized Controlled Trial

Initially, nine subjects (mean age 48 years) were eligible for the study, and three completed the entire 7-week trial. Three subjects dropped out immediately because of nausea and vomiting. Notably, the nausea and vomiting lasted for at least 2 days and was not relieved by dimenhydrinate. Subjects withdrew for a variety of reasons in addition to nausea

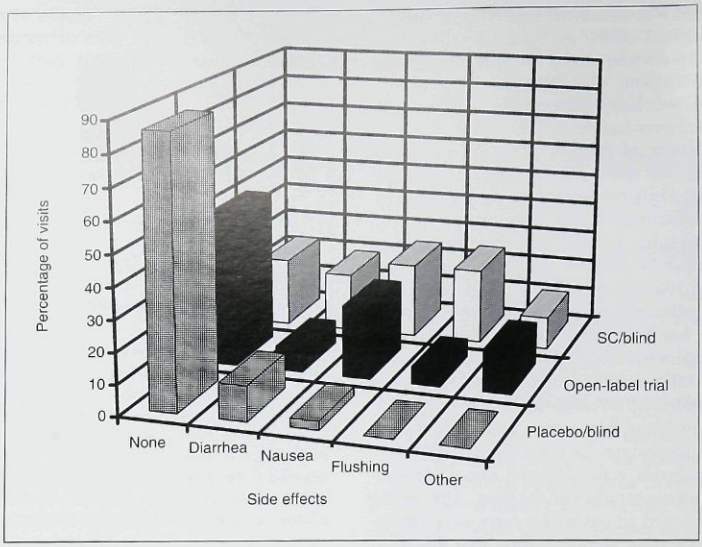

Fig 2 Percentage of visits for which side effects were reported under double-blind conditions where either SC (SC/blind) or placebo (placebo/blind) were administered and in response to SC during open-label administration (open label). Note that in some cases, subjects reported multiple side effects.

Table 2 Report of Recovery for Subjects During the 3 Weeks of Placebo or SC Treatment in the Double-Blind Randomized Trial*

Subject	Condition	No. of visits better	No. of visits same	No. of visits worse
A	Placebo	0	8	0
B	Placebo	0	8	0
C	Placebo	0	8	0
D	Placebo	3	2	3
E	Placebo	3	3	2
A	SC	0	8	0
B	SC	0	6	2
C	SC	4	2	2
F	SC	1	4	3

*Three subjects (A, B, and C) received SC for 3 weeks and the placebo for 3 weeks. There was a possible total of eight visits per subject because no recovery could be reported on the first appointment of any regimen.

and vomiting, including AFP (even while taking SC) that was so severe as to preclude clinic visits, or in one case, the misconception that the subject's flu symptoms were related to the drug. (The latter individual was taking placebo at the time.) None of the subjects who withdrew reported any pain relief at any point in the study. In total, five subjects completed the entire placebo regimen, and four received 3 weeks of SC.

There was a slight increase in the mean of differences in DPS (final minus initial) for both SC and placebo treatment (Fig 1). The increase was greater following SC administration, but neither was found to be significant using the paired Student's *t* test. The digital pain scores throughout the placebo and SC trials are shown in Figs 3 and 4 for all of the subjects who completed these regimens, as well as for the subject who completed 2 of the 3 weeks of SC treatment. There are no discernible trends in either direction for digital pain scores for either the placebo or SC treatments.

Subjective reports of recovery for placebo and SC administration are shown in Table 2 for the

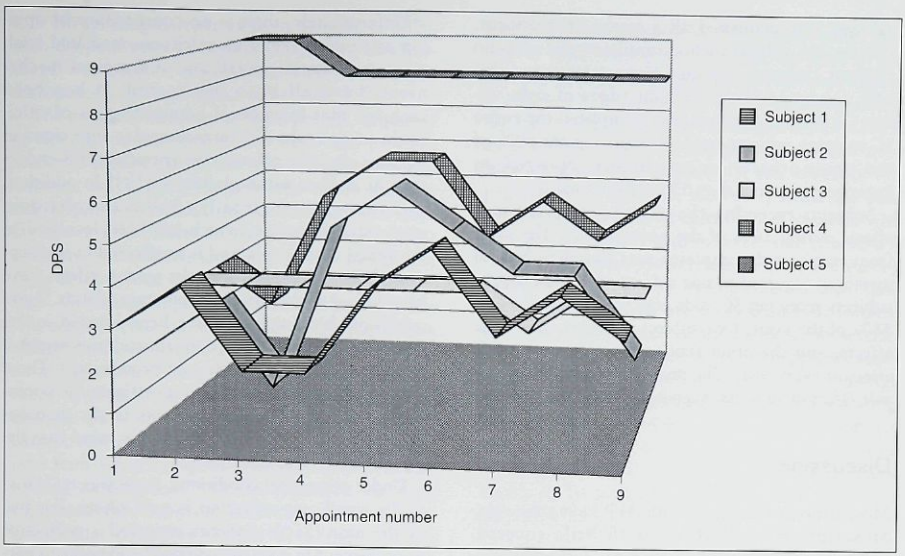

Fig 3 Digital pain scale scores for five subjects during administration of placebo under double-blind conditions. There is no trend toward a reduction or increase in reported pain scores during the 3-week period.

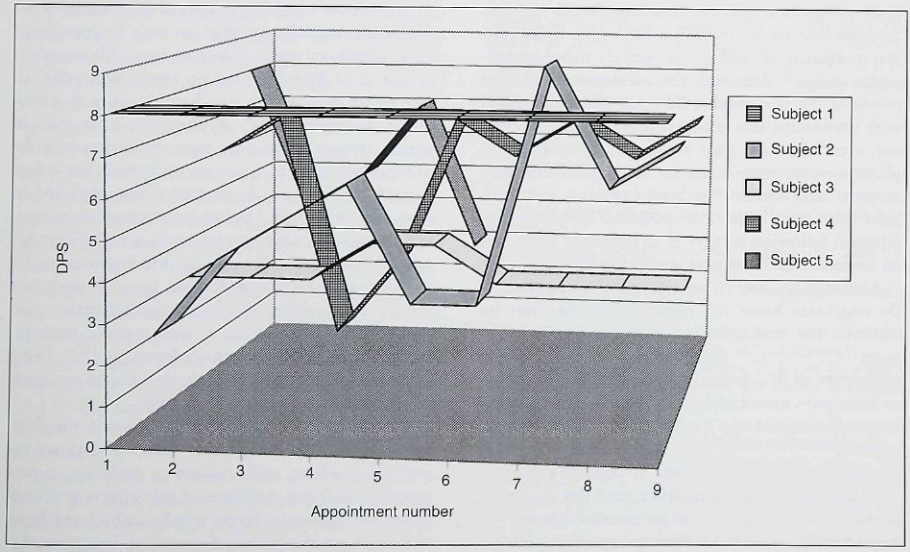

Fig 4 Digital pain scale scores for four subjects who completed 3 weeks of SC administration and one subject who received 2 weeks of SC administration under double-blind conditions. As with the placebo, there was no discernible trend in pain scores.

subjects who competed all 3 weeks of treatment. Of the five subjects who completed the placebo regimen, only two reported improvement and this only occurred 38% of the time (three of eight visits). Of the four subjects who completed the entire SC regimen, one reported an improvement 50% of the time; otherwise, no subject reported an improvement more than 13% of the time.

Subjects receiving the placebo reported side effects during 14% of the visits (Fig 2). The most frequently cited complaint was diarrhea but all instances occurred in one subject. Alternatively, in subjects receiving SC, side effects were reported at 58% of the visits. One subject experienced no side effects, and the other three subjects noted a side effect at every visit. The most frequently occurring side effect in subjects receiving SC was nausea.

Discussion

Most patients presenting with AFP have tried nonprescription medications with little success. Similarly, opioids and nonsteroidal anti-inflammatory medications may be equally ineffective in the management of pain associated with AFP. On the basis of studies implicating a role for depressive illness in AFP and because of their demonstrated analgesic properties, tricyclic antidepressants such as amitriptyline or nortriptyline have also been used for treatment of AFP[5,25] as well as other neuropathic pains.[26] Although the antidepressants have provided the best results, they are often associated with unpleasant side effects that preclude continued use, even when the pain is reduced. In addition to pharmacologic approaches for management of AFP, surgical intervention has been explored, but with poor outcomes. In fact, the potential for pain exacerbation following surgery is so high that surgery is an unreasonable treatment choice for AFP.[10]

Although the use of an agent (SC) that primarily regulates bone cell metabolism may not be obvious for management of pain, there are reports[17,18,20,21,23,27-31] that demonstrate the analgesic properties of SC. Indeed, SC-mediated abrogation of bone pain associated with osteoporosis or other bone diseases (eg, Paget's) has been documented,[17,18,20,21,23,28,29] and these effects occur well in advance of improvements in skeletal integrity. This has led to the suggestion that the analgesic action of SC is distinct from its effects on bone.[18,22] Importantly, reports[14,17,18,22] concerning management of pain suggest that not only is the drug effective in difficult pain conditions, but that side effects are either rare or transitory.

Unfortunately, there is no concordance of opinion as to what underlies calcitonin-mediated analgesia; peripheral, spinal, and supraspinal mechanisms have all been implicated. It has been reported that intrathecal administration of calcitonin in animals and intramuscular injections in humans alter the plasma concentration of ß-endorphin as well as prostaglandin E_2.[32-34] In addition, calcitonin is structurally similar to calcitonin gene–related peptide, which has been localized in the spinal dorsal horn and is implicated in nociception.[35] Finally, central nervous system effects have been linked to the catecholaminergic actions,[36] and calcitonin-binding sites have been located in the raphe nucleus and the periaqueductal gray regions, which are associated with pain processing.[37] These issues underscore the need to investigate the potential usefulness of analgesic agents in the management of AFP, and it was with this in mind that the present study was undertaken.

Under open-label conditions, there was no statistically significant reduction in pain scores, but five of the nine (56%) patients reported a subjective improvement in pain, providing the impetus to perform a randomized controlled trial to determine the analgesic effects of SC on AFP. Because of the incidence and severity of the side effects, however, we were unable to test a sufficient number of subjects to provide an adequate statistical assessment of SC analgesia. Accordingly, this can only be considered an exploratory study. Nevertheless, subcutaneous injection of SC provided no immediate relief of AFP in seven subjects, which contrasts with previous investigations[14,15] of phantom limb pain in which almost immediate pain reduction was reported. However, findings reported for other painful conditions indicate that a longer period of time may be required before pain reduction occurs. For example, it may require up to 8 to 10 days for pain associated with malignant tumors to be reduced with a calcitonin nasal spray,[30] and even longer delays between drug administration and onset of analgesia (1 to 6 weeks) have been reported in osteoporotic crush fractures.[17,18] These factors could explain, in part, the lack of analgesic effect with SC in patients with AFP.

In addition to some variance between the findings reported in the present study and those reported elsewhere, with respect to analgesia, it was apparent that the incidence of side effects was considerably different from what might have been expected on the basis of previous literature reports. For example, dropout rates because of side effects have approximated 10%,[15,18] when SC was used as an analgesic. However, the incidence of

side effects ranged from 10% to as high as 53%, with dropout rates as high as 30% when this hormone was used to manage the bone turnover in osteoporosis or Paget's disease of bone.[20,39]

The apparent discrepancy between the frequency of side effects reported in our study and in other analgesic studies can be interpreted in a number of different ways. First, there is little doubt that the side effects were related to SC because there were far fewer side effects in the subjects taking the placebo. It has been shown that the method of drug delivery can affect the incidence of side effects. Calcitonin appears to be best tolerated when it is administered via nasal spray,[27] but significant side effects have also been noted with this route of administration.[28] Another factor could be that there is something unique about subjects with chronic pain or, specifically, in subjects with chronic refractory pain. One possibility is that subjects with refractory pain demonstrate a tendency toward somatization.[10] In this regard, it has been suggested that subjects with chronic temporomandibular disorders (TMD) have higher scores on the System Checklist-90-Revised, which measures somatization; others have shown that subjects with chronic facial pain tend to have a higher incidence of somatic complaints.[40] If there is a tendency toward somatization in subjects with refractory facial pain (and in this case AFP), this tendency might serve to amplify the side effects that otherwise remain unnoticed or at least tolerable in a less susceptible population. Although not described here, SC was also administered under open-label conditions to six subjects with refractory TMD. It is interesting to note that four of the six (67%) subjects were not able to continue with SC therapy because of severe side effects, which correlates well with data suggesting that this population may have a high degree of somatization characteristics.[40] Indeed, it is possible that a psychologic etiology might also underlie the slight improvement in symptoms when subjects were knowingly taking SC as compared to those taking the medication under blinded conditions. Obviously, further investigation in this area is required, and in this regard, the prevalence of high somatization scores in AFP subjects is currently being explored.

Subjects with AFP apparently do not respond to SC in the same manner as do subjects with other painful conditions. Specifically, no immediate pain relief was reported, and the side effects appeared to be more frequent and severe than previously documented. If these findings can be translated to clinical practice, it appears that SC, as administered using the protocol in the present study, cannot be used reliably to treat AFP. In spite of the fact that the small sample size of this study makes it impossible to formulate a conclusion regarding the effectiveness of SC for management of AFP, it appears that the drug is not efficacious if only because of the high incidence of side effects in this population of subjects. However, while the data suggest that the use of calcitonin in subjects with AFP will necessarily lead to severe side effects, it is conceivable that slower titration of increasing doses of the drug may have precluded this. Similarly, the concurrent use of antinauseant medication may have attenuated the incidence or severity of side effects, but their use in the present study would have been a confounding factor. Although the results of the present study are disappointing, these findings underscore a need for a randomized controlled trial design to illustrate the potential usefulness (or lack thereof) of proposed analgesic agents in the treatment of specific pain conditions such as AFP.

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References

1. Friedman AP. Atypical facial pain. Headache 1969;9:27–30.
2. Loeser JD. Tic douloureux and atypical facial pain. Can Dent Assoc J 1985;51:917–923.
3. Reik L Jr. Atypical facial pain: A reappraisal. Headache 1985;25:30–32.
4. Solomon S, Lipton RB. Atypical facial pain: A review. Semin Neurol 1988;8:332–338.
5. Pfaffenrath V, Rath M, Pollman W, Keeser W. Atypical facial pain—application of the IHS criteria in a clinical sample. Cephalalgia 1993;13:84–88.
6. Graff-Radford SB, Solberg WK. Atypical odontalgia. J Craniomandib Disord Facial Oral Pain 1992;6:260–265.
7. Gratt BM, Sickles EA, Graff-Radford SB, Solberg WK. Electronic thermography in the diagnosis of atypical odontalgia: A pilot study. Oral Surg Oral Med Oral Pathol 1989;68:472–481.
8. Hapak L, Gordon A, Locker D, Shandling M, Mock D, Tenenbaum HC. Differentiation between musculoligamentous, dentoalveolar, and neurologically based craniofacial pain with a diagnostic questionnaire. J Orofacial Pain 1994;8:357–368.

9. Lascelles RG. Atypical facial pain and depression. Br J Psychiatry 1966;112:651–659.
10. Remick RA, Blasberg B, Barton JS, Campos PE, Miles JE. Ineffective dental and surgical treatment associated with atypical facial pain. Oral Surg Oral Med Oral Pathol 1983; 55:355–358.
11. Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? Part I. Oral Surg Oral Med Oral Pathol 1993;75:95–105.
12. Drummond PD. Vascular changes in atypical facial pain. Headache 1988;28:121–123.
13. Bennet GJ. Animal models of neuropathic pain. In: Gebhart GE, Hammond DL, Jensen TS (eds). Proceedings of the Seventh World Congress on Pain: Progress in Pain Research and Management. Seattle: IASP Press, 1993:495–510.
14. Fiddler DS, Hindman JB. Intravenous calcitonin alleviates spinal anesthesia-induced phantom limb pain. Anesthesiology 1991;74:187–189.
15. Jaeger H, Maier C. Calcitonin in phantom limb pain: A double-blind study. Pain 1992;48:21–27.
16. Deftos LJ. Calcitonin. In: Flavus MJ (ed). Primer on Metabolic Bone Disease and Disorders of Mineral Metabolism, ed 2. New York: Raven Press, 1993:76–80.
17. Lyritis GP, Tsakalakos N, Magiasis B, Karachalios T, Yiatzides A, Tsekoura M. Analgesic effect of salmon calcitonin in osteoporotic vertebral fractures: A double-blind placebo-controlled clinical study. Calcif Tissue Int 1991; 49:369–372.
18. Gennari C, Agnusdei D. Calciotropic hormones and pain. Contrib Nephrol 1991;91:86–94.
19. Galli G, Gordon A, Shandling M, Mock D, Tenenbaum HC. Diagnostic and prognostic features of atypical facial pain: A pilot study [abstract]. J Orofacial Pain 1993;7:116.
20. Grunstein HS, Clifton-Bligh P, Posen S. Paget's disease of bone: Experiences with 100 patients treated with salmon calcitonin. Med J Aust 1981;2:278–280.
21. Gennari C, Agnusdei D, Camporeale A. Use of calcitonin in the treatment of bone pain associated with osteoporosis. Calcif Tissue Int 1991;49(suppl):S9–S13.
22. Singer FR. Clinical efficacy of salmon calcitonin in Paget's disease of bone. Calcif Tissue Int 1991;49(suppl):S7–S8.
23. Rifat SF, Kiningham RB, Peggs JF. Calcitonin in the treatment of osteoporotic bone pain. J Fam Pract 1992;35: 93–96.
24. Schwartz D, Flamant R, Lellouch J. Clinical Trials. London: Academic Press, 1980.
25. Kreisberg MK. Tricyclic antidepressants: Analgesic effect and indications in orofacial pain. J Craniomandib Disord Facial Oral Pain 1988;2:171–177.
26. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, Dubner R. Efficacy of desipramine in painful diabetic neuropathy: A placebo-controlled trial. Pain 1991;45:3–9.
27. Tolino A, Romano L, Ronsini S, Riccio S, Montemagno U. Treatment of postmenopausal osteoporosis with salmon calcitonin nasal spray: Evaluation by bone mineral content and biochemical patterns. Int J Clin Pharmacol Ther Toxicol 1993;31:358–360.
28. Pontiroli AE, Pajetta E, Calderara A, Alberetto M, Pozza G, Manganelli V, et al. Intranasal and intramuscular human calcitonin in female osteoporosis and in Paget's disease of bone: A pilot study. J Endocrinol Invest 1991; 14:47–51.
29. Pecile A. Calcitonin and relief of pain. Bone Miner 1992; 16:187–189.
30. Szánto J, Ady N, Jozsef S. Pain killing with calcitonin nasal spray in patients with malignant tumors. Oncology 1992;49:180–182.
31. Wallach S. The role of calcitonin treatment in postmenopausal osteoporosis. Orthop Rev 1992;21:1130–1131.
32. Laurian L, Oberman Z, Graf E, Gilad S, Hoerer E, Simantov R. Calcitonin induced increase in ACTH, ß-endorphin and cortisol secretion. Horm Metab Res 1986;18:268–271.
33. Üstdal M, Dogan P, Soyuer A, Terzi S. Treatment of migraine with salmon calcitonin: Effects on plasma ß-endorphin, ACTH, and cortisol levels. Biomed Pharmacother 1989;43:687–691.
34. Franceschini R, Cataldi A, Cianciosi P, Garibaldi A, Corsini G, Barreca T, Rolandi E. Calcitonin and ß-endorphin secretion. Biomed Pharmacother 1993;47:305–309.
35. Candeletti S, Ferri S. Antinociceptive profile of intracerebroventricular salmon calcitonin and calcitonin gene-related peptide in the mouse formalin test. Neuropeptides 1990; 17:93–98.
36. Guidobono F, Netti C, Pagani F, Sibilia V, Pecile A, Candelleti S, Ferri S. Relationship of analgesia induced by centrally injected calcitonin to the CNS serotonergic system. Neuropeptides 1986;8:259–271.
37. Olgiati VR, Guidobono F, Netti C, Pecile A. Localization of calcitonin binding sites in rat central nervous system: Evidence of its neuroactivity. Brain Res 1983;265:209–215.
38. Gennari C, Passeri M, Chierichetti SM, Piolini M. Side effects of synthetic salmon and human calcitonin. Lancet 1983;1(8324):594–595.
39. Carrozzo M, Cantatore FP, D'Amore M, Pipitone V. Side effects of calcitonin therapy. Clin Trials J 1988;25:87–88.
40. Massoth DL, Dworkin SF, LeResche L, Harrison RH, Whitney CW, Wilson L, et al. Non-specific physical symptom scores and temporomandibular disorders [abstract 1690]. J Dent Res 1995;74:223.

Resumen

Efectos del Calcitonin Salmón en Pacientes con Dolor (Idiopático) Facial Atípico: Un Ensayo Fortuito Controlado

Las propriedades analgésicas del calcitonin salmón en el tratamiento del dolor facial atípico (DFA) fueron investigadas. Un ensayo inicial de "etiqueta abierta" del calcitonin salmón en pacientes con DFA refractario, fue seguido de un ensayo subsequente fortuito, a ciegas, controlado con placebo, y cruzado, del calcitonin salmón en el manejo del DFA. El calcitonin salmón (en dilución de 100 UI en 1 mL de solución salina) ha sido administrado a manera de etiqueta-abierta a trece pacientes con DFA refractario utilizándo un régimen de cinco días por semana por un período de seis semanas. En la investigación fortuita subsequente, el calcitonin salmón (en dilución de 100 UI en 1 mL de solución salina) o el placebo (1 mL de solución salina) ha sido administrado tres veces por semana por un período de tres semanas cada uno, seguido de un período de "lavado" prévio al cruzamiento. El porcentaje de los individuos que se retiráron del estudio (57%) excedió los reportados por otros estudios sobre el dolor utilizándo el calcitonin, y en consequencia, ha sido imperativo parar el estudio por razones éticas. No hubo cambio alguno en las medidas consequentes ($P > .05$) tanto en los pacientes tratados con droga activa como en los pacientes tratados con placebo y la gran incidencia de efectos colaterales bajó el número de pacientes que tomaban el calcitonin salmón. Aunque el calcitonin salmón puede tener propriedades analgésicas, no es una droga eficaz para DFA, mayormente debido a sus efectos colaterales.

Zusammenfassung

Die Auswirkungen von Lachs-Calcitonin auf Patienten mit atypischen Gesichtsschmerzen: eine randomisierte kontrollierte Studie

Es wurde die schmerzlindernde Wirkung von Lachs-Calcitonin für die Behandlung atypischer Gesichtsschmerzen (AFP) getestet Einem ersten offenen Versuch mit Lachs-Calcitonin bei Patienten mit hartnäckigem AFP ist eine randomisierte Doppelblindstudie gefolgt. Das Lachs-Calcitonin (LC) wurde 13 Patienten mit hartnäckiger AFP 5 mal pro Woche 6 Wochen lang gegeben In der darauffolgenden Studie wurde LC oder Placebo (Kochsalzlösung) für 3 Wochen 3 mal pro Woche verabreicht. Für die Beurteilung der Ergebnisse wurden die VAS, die Selbsteinschätzung der Schmerzlinderung und die Nebenwirkungen gemessen. Der Prozentsatz der Patienten, die die Studie unterbrachen (57%) war höher als bei anderen Studien mit Calcitonin. Es wurden keine unterschiedlichen Werte bezüglich Medikament oder Placebo gemessen ($P > .05$), eine hohe Inzidenz der Nebenwirkungen zwang Patienten, die Lachs-Calcitonin zu sich nahmen, die Studie zu unterbrechen. Obwohl LC schmerzlindernde Wirkungen haben könnte, ist es nicht für AFP indiziert, hauptsächlich wegen der verursachten Nebenwirkungen.