Effect of Calcitonin on Healing Duration, Function and Pain Relief in Patients with Maxillofacial Fractures. A pilot study

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ABSTRACT

Introduction: Calcitonin is a polypeptide hormone regulating the metabolism calcium in the body. Many studies showed that calcitonin had analgesic effect on several painful circumstances. The aim of this study was to determine the effects of intranasal calcitonin during the immediate postoperative period on postoperative pain in patients undergoing maxillofacial fracture surgery.

Materials and Methods: In this clinical trial which was conducted in April 2019 in Imam Reza Hospital of Tabriz, 16 patients with maxillofacial fracture were divided randomly into two groups. The intervention group was given 200UI of intranasal calcitonin and the control group received nasal spray of NaCl. The severity of pain was then evaluated daily for up to seven days after the operation, with the severity of: no pain (0) to the most severe pain (10) using visual analog scale for pain. The daily dose of analgesic was also measured. The patients were allowed to request 250 mg of injectable acetaminophen each day up to a maximum daily dose of 4 g (maximum permissible dose) in the event of pain. Results: The results show that the pain intensity between two groups was not significantly different. However in the seventh day the total acetaminophen consumption was significantly lower in the intervention group. Conclusion: calcitonin may be a useful medication to help to control the post operative pain by reducing the required dose of routine painkillers.

INTRODUCTION

During maxillofacial surgeries, local anesthesia infiltration when combined with general anesthesia (GA) provides good operative condition but has relatively shorter duration of postoperative analgesia. So various adjuvants like opioids, clonidine, dexamethasone, ketamine, etc., were used post operatively to better control of pain (1).

Salmon calcitonin is a straight-chain, amidated peptide hormone with a seven-membered disulphide ring at the N-terminus. Calcitonin was discovered in 1962 by Dr. D. H. Copp, from the thyroid glands of the dog (2). Regardless of the species of origin, all calcitonins consist of a chain of 32 amino acids. Seven of the first nine residues are common to all species, with considerable sequence variability in the rest of the molecule. In 1968, calcitonin was isolated from the ultimobranchial glands of the salmon (3), and it was subsequently shown that salmon calcitonin has a relative potency in man that is approximately 20- to 50-fold greater than that of human calcitonin. This increased potency is partly due to the greater half-life in circulation compared to human calcitonin, but could also be due to higher receptor affinity for the salmon molecule. Because of this higher potency and longer half-life in circulation, salmon calcitonin is the most frequently used calcitonin in human therapy (4).

In addition to the maintenance of BMD, inhibition of bone turnover, and reduction of fracture rate, calcitonin has been shown to have a direct beneficial effect on pain reduction, and therefore is clinically useful in several diseases that involve bone pain. There is preliminary evidence that calcitonin may have a beneficial effect on the pain and inflammation associated with osteoarthritis (5) Calcitonin has also been shown to relieve unrelated sources of pain such as phantom limb pain (6) as well as pain associated with vertebral fracture, malignant bone metastases, Paget’s disease, and Reflex Sympathetic Dystrophy Syndrome (7). The observation by Gennari that the analgesic effect of calcitonin does not correlate temporally with its effect on calcium lowering suggested that the analgesic properties of calcitonin appear to be independent of its effects on osteoclasts (8). Calcitonin is the only currently used therapy for the treatment of osteoporosis with the added advantage of relieving bone pain. This unique feature provides a further rationale for the clinical use of calcitonin for pain reduction following osteoporotic fractures, as well as other pain syndromes.
Previous studies have not investigated the efficacy of calcitonin to control post operative pain in healthy patients with maxillofacial fractures. We postulated that intranasal administration of calcitonin in patients undergoing maxillofacial surgeries will significantly reduce the postoperative pain. Thus, the aim of this study was to determine the effects of intranasal calcitonin during the immediate postoperative period on postoperative pain in patients undergoing maxillofacial fracture surgery.

Aims
A- General goals:
Effect of calcitonin on post-operative pain in patients with maxillofacial fractures.

B- Specific objectives:
1. Comparing the post operative pain intensity in intervention group (receiving 200 IU of intranasal calcitonin) and control group (NaCl serum nasal spray)
2. Comparing the total daily dose of acetaminophen consumption in intervention group (receiving 200 IU of intranasal calcitonin) and control group (NaCl serum nasal spray).

C- Hypothesis
1- The post operative pain intensity in intervention group (receiving 200 IU of intranasal calcitonin) and control group (NaCl serum nasal spray) are not significantly different.

Methods and materials:

Inclusion Criteria
1. Obtaining informed consent
2. All patients with maxillofacial fracture which happened within less than a week.

Exclusion Criteria
1. Systemic conditions impairing wound healing
2. Patient mental illness
3. Allergy to calcitonin
4. Calcium metabolism disorder.

This pilot clinical trial study was performed on patients with maxillofacial fracture referring to the maxillofacial surgery clinic and emergency department of Imam Reza Hospital in Tabriz during the April 2019. Considering the different surgical techniques in the upper and lower jaw, and also in different methods of fixation, the participants in this study first clearly were classified based on fracture area and number, extension and methods of surgical approaches and fixation. Each group was divided into two intervention and control groups in a simple randomized manner. Then, the blinded control group received normal saline serum nasal spray and the blinded intervention received group 200 units of calcitonin nasal spray daily from the time of the patients’ surgery to the completion of the treatment period. The severity of pain was then evaluated daily for up to seven days after the operation, with the severity of: no pain (0) to the most severe pain (10) using visual analog scale for pain. The daily dose of analgesic were also measured. The patients were allowed to request 250 mg of injectable acetaminophen each day up to a maximum daily dose of 4 g (maximum permissible dose) in the event of pain. Before entering the study, the level of serum calcium and was measured and patients were evaluated for calcitonin sensitivity. In several studies calcitonin had been used to control pain without the presence of osteoporosis. In most studies, the complications of calcitonin use were mild and tolerable, and in case of symptoms, the main complaint was the nausea. Therefore, in the event of complications arising from the drug, the medication was stopped and consultation with the endocrinologist was performed.

Participants
All patients with maxillofacial fracture which happened within less than a week will be included in the study. The patients with systemic conditions impairing wound healing, patients with mental illness history of allergy to calcitonin and calcium metabolism disorder were excluded. Intervention group received 200 unit of intranasal calcitonin and control group was given nasal spray of NaCl spray. Randomization was performed in simple manner.

Outcomes
The primary outcome in this study was the post operative pain relief. Participants in this study were divided into two groups. Intervention group received 200 unit calcitonin nasal sprays after surgery and the control group received normal saline serum nasal spray. The severity of pain was then evaluated daily for up to seven days after the operation, with the severity of: no pain (0) to the most severe pain (10) using visual analog scale for pain. The daily dose of analgesic was also measured. The patients were allowed to request 250 mg of injectable acetaminophen each day up to a maximum daily dose of 4 g (maximum permissible dose) in the event of pain. The difference in analgesic consumption was the secondary outcome.

All patients received the routine treatment plan, and none of the patients was deprived of routine treatment. All ethical aspects of the study were reviewed and approved by the Medical Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1396.1270).

Statistical Analysis
The results of the study will be reported using descriptive methods such as mean ± standard deviation, frequency (percent). To compare the pain values in the two groups, if the data distribution is normal, independent sample T-test is independent and if not non-parametric mann–whitney u test was used. Normality of the data was checked using the Kolmogorov-Smirnov test. The analysis was performed using SPSS 17 software and p <0.05. was considered significant.

RESULTS
In this pilot study on the 16 patients the Chi-square test and independent t-test didn’t show a statistically significant dif-
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Table 1. Daily mean VAS Score

|                | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|----------------|-------|-------|-------|-------|-------|-------|-------|
| Placebo        | 8.36  | 7.36  | 5.36  | 4.36  | 3.36  | 2.16  | 1.32  |
| Calcitonin     | 8.05  | 7.50  | 5.05  | 4.50  | 3.16  | 2.38  | 1.53  |
| p value        | 0.371 | 0.826 | 0.579 | 0.605 | 0.376 | 0.856 | 0.979 |

Table 2. Acetaminophen consumption for the 7th day

|                | Calcitonin | Placebo |
|----------------|------------|---------|
| Sample size    | 8          | 8       |
| Arithmetic mean| 250.0000   | 1750.0000|
| 95% CI for the mean | -65.9862 to 565.9862 | 1434.0138 to 2065.9862 |
| Standard deviation | 377.9645 | 377.9645 |
| Standard error of the mean | 133.6306 | 133.6306 |
| Difference     | 1500.0000  |         |
| Pooled Standard Deviation | 377.9645 |             |
| Standard Error | 188.9822   |         |
| 95% CI of difference | 1094.6734 to 1905.3266 |           |
| Two-tailed probability | p<0.0001 |             |

ference (p value> 0.05) between the participants in the fracture site and mean age of the patients respectively. In other words, the patients in the two groups were homogenous in terms of gender distribution, mean age, and type of fracture.

Table 1 shows the average pain severity in the study groups at different times. As you can see, the intensity of the pain is the highest immediately after consciousness, but gradually decreases within 7 days.

Samples T Test Independent test was used to evaluate the effect of calcitonin on the mean pain intensity in each study groups. The results of this test showed that in days 1, 2, 3, 4, 5, 6, and 7 after surgery, the mean pain intensity was not significantly different between the intervention and control group. (p-value > 0.05).

The amount of analgesic used during 7 days after was recorded for each group. The results showed that in the calcitonin spray group, the amount of analgesic used was lesser than the control group in day 7 (Table 2). However, independent t-test showed that the daily total amount of analgesic consumption in day 1, 2, 3, 4,6 and 6 between two groups was not significantly different (p Value > 0.05).

DISCUSSION

In our study the effect calcitonin on the pain intensity and analgesic consumption was investigated on the 16 participants who suffered from maxillofacial fracture. Intervention group received 200 unit of calcitonin nasal spray after surgery, and the control group received normal saline serum nasal spray. The severity of pain is then evaluated daily for up to seven days after the operation, using visual analog scale for pain. The daily dose of analgesic is also was measured. The patients were allowed to request 250 mg IV infusion of acetaminophen each day up to a maximum daily dose of 4 g. The results show that the pain intensity between two groups was not significantly different. However, in the seventh day the total acetaminophen consumption was significantly lower in the intervention group (Table 2). This result shows that calcitonin may be a useful medication to help to control the post operative pain by reducing the required dose of routine painkillers. Thus benefits from using a short course of calcitonin in the treatment of maxillofacial fractures pain include adequate and timely pain relief, as well as earlier functional rehabilitation. These specific effects of calcitonin have not been previously presented in medical literature. Limitations to our study include the small sample size which nonetheless led to a homogenous patient sample with all the advantages that this could carry.

CONCLUSION

This study showed that calcitonin may be a useful medication to help to control the post operative pain by reducing the required dose of routine painkillers.

REFERENCES

1. Mandal D, Das A, Chhaule S, Halder PS, Paul J, Roy-Basunia S, et al. The effect of dexmedetomidine added to preemptive (2% lignocaine with adrenaline) infiltration on intraoperative hemodynamics and postoperative pain after ambulatory maxillofacial surgeries under general anesthesia. Anesth Essays Res. 2016;10(2):324-31. Epub 2016/05/24.
2. Lyritis GP, Trovas G. Analgesic effects of calcitonin. Bone. 2002;30(5 Suppl):71S-4S. Epub 2002/05/15.
3. Braga PC. Calcitonin and its antinociceptive activity: animal and human investigations 1975-1992. Agents Actions. 1994;41(3-4):121-31. Epub 1994/05/01.
4. Yeh CB, Weng SJ, Chang KW, Chan JY, Huang SM, Chu TH, et al. Calcitonin alleviates hyperalgesia in osteoporotic rats by modulating serotonin transporter activity. Osteoporos Int. 2016;27(11):3355-64. Epub 2016/06/05.

5. Chesnut CH, 3rd, Azria M, Silverman S, Engelhardt M, Olson M, Mindeholm L. Salmon calcitonin: a review of current and future therapeutic indications. Osteoporos Int. 2008;19(4):479-91. Epub 2007/12/12.

6. Viana R, Payne MW. Use of calcitonin in recalcitrant phantom limb pain complicated by heterotopic ossification. Pain Res Manag. 2015;20(5):229-33. Epub 2015/08/21.

7. Appelboom T. Calcitonin in reflex sympathetic dystrophy syndrome and other painful conditions. Bone. 2002;30(Suppl):84S-6S. Epub 2002/05/15.

8. Gennari C, Bocchi L, Orso CA, Francini G, Civitelli R, Maioli E. The Analgesic Effect of Calcitonin in Active Paget’s Disease of Bone and in Metastatic Bone Disease. Orthopedics. 1984;7(9):1449-52. Epub 1984/09/01.

9. Sarveravan P, Astaneh B, Shokrpour N. Adherence to the CONSORT Statement in the Reporting of Randomized Controlled Trials on Pharmacological Interventions Published in Iranian Medical Journals. Iran J Med Sci. 2017;42(6):532-43. Epub 2017/12/01.