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REVIEW ARTICLE

Calcitonin as an analgesic agent: review of mechanisms of action and clinical applications☆

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Abstract
Background and objectives: Calcitonin is a polypeptide hormone regulating the metabolism of calcium in the body. For many years calcitonin has been used to maintain and improve bone mineral density and to reduce the fracture rate. Many studies showed that calcitonin had analgesic role in several painful circumstances. This pain-ameliorating effect is irrelevant to its osteoclastic inhibitory effect and mechanisms like altering Na+ channel and serotonin receptor expression or hypothesis including the endorphin-mediated mechanism were used to explain this effect. In this study we performed a thorough review on the role of calcitonin as an analgesic agent in different scenarios and investigated the fact that calcitonin can be a feasible medication to relieve pain.
Method: Many studies focused on the analgesic effect of calcitonin in several painful circumstances, including acute pains related to vertebral fractures, metastasis, migraine and reflex sympathetic dystrophy as well as neuropathic pains related to spinal injuries or diabetes, and phantom pain. Also, calcitonin was showed to be a useful additive to local anesthesia in the case of controlling postoperative pain or trigeminal neuralgia more effectively. However we faced some contradictory data for conditions like lumbar canal stenosis, complex regional pain syndrome, phantom pain and malignancies.
Conclusion: This study showed that calcitonin could be helpful analgesic agent in different painful situations. Calcitonin can be considered an eligible treatment for acute pains related to vertebral fractures and a feasible alternative for the treatment of the acute and chronic neuropathic pains where other medications might fail.

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PALAVRAS-CHAVE
Calcitonina;
Dor aguda;
Dor crônica;
Fraturas vertebrais;
Malignidade;
Enxaqueca;
Dor fantasma;
Neuropatias diabéticas

Calcitonina como agente analgésico: revisão dos mecanismos de ação e das aplicações clínicas

Resumo
Justificativa e objetivos: A calcitonina é um hormônio polipeptídico que regula o metabolismo do cálcio no organismo. Por muitos anos a calcitonina tem sido usada para manter e melhorar a densidade mineral óssea e reduzir a incidência de fraturas. Muitos estudos mostraram que a calcitonina teve efeito analgésico em várias condições físicas de dor. Esse efeito de melhoria da dor é irrelevante diante de seu efeito inibidor osteoclástico e de mecanismos, tais como a alteração do canal de Na+ e da expressão do receptor de serotonina, incluindo a hipótese do mecanismo mediado pela endorfina, que foram usados para explicar esse efeito. Neste estudo, fizemos uma revisão completa sobre o papel da calcitonina como agente analgésico em diferentes cenários e investigamos o fato de que a calcitonina pode ser uma medicação viável para aliviar a dor.
Método: Muitos estudos centraram no efeito analgésico da calcitonina em várias condições de dor, incluindo dores agudas relacionadas a fraturas vertebrais, metástases, enxaqueca e distrofia simpática reflexa, bem como dores neuropáticas relacionadas a lesões medulares ou ao diabetes e dor fantasma. Além disso, a calcitonina mostrou ser um aditivo útil à anestesia local para o controle mais efecaz da dor pós-operatória ou neuralgia do trigêmeo. Porém, nos deparamos com alguns dados contraditórios em condições como estenose do canal lombar, síndrome complexa da dor regional, dor fantasma e malignidades.
Conclusão: Este estudo mostrou que a calcitonina pode ser um analgésico útil em diferentes condições de dor. A calcitonina pode ser considerada um tratamento elegível para as dores agudas relacionadas a fraturas vertebrais e uma opção viável para o tratamento das dores neuropáticas agudas e crônicas em que outros medicamentos podem falhar.

Introduction

The primary role of polypeptide hormone of calcitonin is the controlling bone calcium metabolism and calcium blood levels in the body. For many years calcitonin have been used to maintain and improve bone mineral density and reduce the fracture rate.[1] However various studies showed that calcitonin could have analgesic role in different painful states.[1–5] The anti-nociceptive properties of calcitonin were first reported in 1975, when calcitonin was given through the cerebroventricular route to rabbits.[6] The ability of calcitonin to relieve pain should be irrelevant to the osteoclastic inhibitory effect and may involve other mechanisms which are discussed later.[7,8]

Many studies support the fact that calcitonin showed analgesic effect in several painful circumstances, including metastasis, painful diabetic neuropathy, migraine and reflex sympathetic dystrophy as well as neuropathic pains.[9] It is also used to manage acute pain related to vertebral fractures secondary to osteoporosis, postoperative pains and so on.[1,9,10] However after carefully reviewing the related studies, we faced many contradictory situations in different painful conditions like lumbar canal stenosis, complex regional pain syndrome, phantom pain and malignancies. Also we included many newly emerged clinical applications for calcitonin which were not reviewed and discussed in pervious review articles. For example, using calcitonin as an additive for local anesthesia[11] or using calcitonin to control pain in different syndromes.[12] Also in recent years calcitonin was used as analgesic agent in for many conditions and diseases which again were not included in previous review articles. These conditions include MCcune Albright syndrome, Camurati-Engelmann disease, diabetic neuropathy, postoperative pain, spinal cord related neuropathy, trigeminal nerve neuropathy, migraine, adhesive shoulder, adhesive capsulitis, lumbar canal stenosis, phantom limb pain and comparison of calcitonin with other medications for treating pain.

After searching through online data bases, we found two reviews investigated the analgesic effect of calcitonin. Appelboom reviewed the situations including cancer metastases, osteoporotic fractures, phantom limb pain, complex regional pain syndrome and migraine. Their study suffered from lack of well-designed studies with long-term follow- ups and did not include many conditions which were discussed in our study.[9] Mehta also came up with a well-designed, comprehensive and informative review. But there review just focused on the pain with origin of bone and did not study other types of painful conditions.[4] So as the novelty of this review we are up to investigate the role of calcitonin as an analgesic agent in different painful situations by discussing the mechanism, comparing and evaluating contradictory results, including and gathering newly published data which were not reviewed before and finally drawing a clear outline for possible role of calcitonin as a feasible alternative for pain control by weighting

its effectiveness against its side effects in different painful conditions.

Methods

In this narrative review we investigated all conditions where calcitonin was used as an analgesic agent. To identify the relevant studies we assigned ''pain, analges*, calcitonin'' as the keywords for searching online data bases. First, we searched Cochrane library (1977–present), MEDLINE (1966–present), Scopus (1966–present) and Google scholar (1966–present). All databases were rechecked in June 2019. Also, the reference sections of all relevant studies were checked for further studies.

Then all potentially relevant studies underwent screening of titles and abstracts. Finally the full texts of the all potential articles were retrieved.

The inclusion criteria for this study were:

- The intervention included using calcitonin.
- The pain intensity was measured as outcome.
- The study investigated the painkilling mechanisms of calcitonin.

All types of studies including systematic and narrative reviews, animal studies, clinical trials and case reports were included in this review. For the quality assessment the adherence of the systematic reviews to PRISMA principals and clinical trials to CONSORT principals were assessed. If a study did not follow the principles, the possible effects on outcomes were discussed based on the results of other studies investigating the same topic.

Mechanisms

Several researches have helped reveal the mechanism of the analgesic effects of calcitonin by using different methods and animal pain models.

One theory focuses on the interaction of calcitonin with peripheral neuropathy. According to this theory, chemotherapy-mediated peripheral neuropathy may induce expression of transient receptors like melastatin-8 and ankyrin-1. It was showed that calcitonin could inhibit the signals associated with this receptor(melastatin-8 and ankyrin-1) which contributes to analgesic function of calcitonin in peripheral neuropathy.[13] Also, according to another theory nerve injuries can activate an unknown calcitonin-dependent signal. This signal which is activated by calcitonin administration, results in decreased transcription of the sodium channel in dorsal root ganglion neurons. Therefore calcitonin can regulate primary afferent nerves excitability in peripheral nervous tissues by controlling the transcription of the sodium channel. The signals of calcitonin may be normally inactive due to the absence of a target, whereas nerve injuries or ovariectomy can induce these targets.[14] According to next theory and based on serotonin role in pain processing and modulation, calcitonin has been shown to decrease serotonin transporters and increase the expression of the serotonin receptors of the thalamus.[15] In conclusion, the obtained findings show that calcitonin can alter the channel or receptor expression and therefore relieve lower back pains in patients with neuropathic pains and osteoporosis.[8,15]

Another hypothesis is the endorphin-mediated mechanism; elevated level of endorphin was reported in patients receiving calcitonin.[7] Also an increase in the amount of endorphin, adrenocorticotropic hormone and corticosteroid hormones in serum was shown as the result of application of calcitonin in patients with migraine.[16]

Also inhibiting inflammation mediator substances, including thromboxane and prostaglandins, seems to be another possible peripheral mechanism of action of calcitonin. These findings are based on the seemingly dose-dependent anti-inflammatory effect observed in all the classical animal models.[7]

Another study investigating the role of calcitonin in migraine showed that in trigeminal nucleus caudalis, calcitonin exerted analgesic impacts through inhibiting the c-fos expression and thereby suppressed the activation of trigeminovascular system. Moreover, calcitonin reversed the increase in calcitonin gene-associated peptide of meningeal superfusates and neurons of trigeminal ganglion. The calcitonin pretreatment also inhibited the degranulation of mast cell in meninges. The stabilizing impacts of calcitonin on dural mast cells also contributed to calcitonin analgesic effects.[1]

Vertebral fracture

Vertebral fracture is an osteoporosis-associated fracture with potentially severe pain often requiring bed rest and medications. Using calcitonin for treatment of fracture related pains has been suggested in literatures.[17,18]

The combined results obtained from thirteen trials (n = 589) in a meta-analysis by Knopp and Sihota showed that calcitonin significantly alleviated acute pains in recently-emerging osteoporotic vertebral compression fractures. Rest pain was alleviated within a week and continued to improve within 4 weeks. The differences between the scores of pain and mobility were found to be even greater in the 4th week. The difference in pain score at rest between the groups of the patients suffered from chronic phase was slight and insignificant after 6 months.[17]

Also Blau, in another systematic review based on 14 published studies, in line with Knopp and Sihota's study, showed that calcitonin was clearly a viable option in relieving the pain of the acute vertebral fractures. They also showed that intranasal calcitonin provided a similar degree of analgesia as the parenteral administration with better tolerability, and concluded that calcitonin was viable option for many patients who were unable to tolerate narcotics or Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).[18]

In conclusion, calcitonin can be considered as an eligible treatment for acute pain due to vertebral fracture while it may be less useful in treating chronic pain in vertebral fractures.[17]

Lumbar canal stenosis

Terashima et al.[14] in their study on the rats showed that calcitonin could effectively reduce radicular pain which is a common complaint in lumbar spinal canal stenosis and

lumbar disk herniation. After exposing the L5 nerve root and ligating it extradurally, the rats were given salmon calcitonin systemically. In spite of treatment-resistant nature of radicular pain and its progression to chronic neuropathies, samples showed significant improvements on days 5 and 9.[14] Also sodium channels expression levels which were increase before treatment in the rats with radicular pain, decreased to the normal levels in response to calcitonin. The author concluded that calcitonin could be a therapeutic choice for long-term treatment of radicular pain.[14]

Also in a study by Ashraf on the 36 patients with lumbar spinal canal stenosis showed that patients with severe pain at the start of study, showed significant improvement in pain scores. They gave patients 100 IU of calcitonin four times a month intramuscularly. However patients with mild to moderate pain did not show significant improvement in pain and functional scores.[19]

Haddad in a study on 90 participants with canal stenosis compared the efficacy of 200 IU of nasal calcitonin once daily with gabapentin 300 mg 3 times a day. After 8 weeks patients showed statistically significant better results of improvement in pain and functional scores in calcitonin group than the gabapentin group.[20] However Podichetty could not find any benefits for 200 IU of nasal spray of calcitonin in comparison to placebo in 55 patients with lumbar spinal canal stenosis with the VAS of 6 or higher. The patients received the treatment for 6 weeks and both pain and functional scores were not different significantly.[21] Also Tafazal achieved the same results on 40 patients after 4 weeks.[22]

Based on these studies we can conclude that calcitonin can take part in lumbar canal stenosis treatment as an additional treatment.[19,20] Also Terashima's study demonstrated the molecular mechanism which calcitonin employed to alleviate radicular pain in animal model.[14]

Radius fracture

Karponis et al.[23] investigated the pain-killing effect of calcitonin nasal spray on the post-distal radius fracture. This randomized prospective double-blind trial randomly assigned 41 conservatively-treated female patients with distal radius fracture into two groups, one receiving intranasal calcitonin (200 IU per day) and the other placebo everyday for 3 months. Results showed that calcitonin-mediated pain-killing effects were observed in the early period after post-fracture period as soon as 10 days in comparison to the placebo group. So calcitonin may help controlling the acute pain in the patients with osteoporotic distal radius fractures treated conservatively.[23]

Adhesive capsulitis

Adhesive capsulitis is considered a common problem of the shoulder. It involves the non- osseous parts of glenohumeral joint. The common lists of symptoms are restricted motions, pain during activities and disability in everyday activities.

In a double-blind randomized clinical trial conducted by Rouhani et al. on 64 patients with shoulder adhesive capsulitis, the intervention group received intranasal calcitonin for 6 weeks. Considerable improvements were reported in functional scores and shoulder pain in the calcitonin group in comparison to the placebo group.[24] Also a prospective research by Waldburger on 50 patients with the same disease in three hospitals in Switzerland showed that using calcitonin intranasaly mitigated the pain and improved shoulder function.[25] Brue also found that subcutaneous calcitonin combined with 21 day physiotherapy showed promising effects on adhesive capsulitis.[26]

Malignancy

Metastatic bone disease is a frequent complication in patients with neoplasm. Progression of malignant tumors, especially their infiltration into bones accompanying with developing osteolytic metastases, often causes severe pains. Many patients with high grade malignant tumors (more than 60%) have significant pain.[27]

In a Cochrane review of using calcitonin to control the pain associated with bone metastasis, 2 eligible studies were selected for analysis after screening the databases. A study found calcitonin to exert non- significant effects on total pain relief. Another study found no evidence for calcitonin to reduce pain killer dose in participants with painful metastasis to bones. No evidence was therefore suggested for the effectiveness of calcitonin for controlling complications related to bone metastasis to enhance quality of life and affect patient survival.[28] This review however just included the studies with follow up sessions longer than 2 months. So the short term efficacy and effectiveness of calcitonin as an analgesic agent might be neglected. Therefore many studies emphasizing on the acute-pain-relieving characteristic of calcitonin were not investigated by this review.

Most of the studies supporting the usefulness of calcitonin involved patients with active metastatic disease and a severe intractable pain (Table 1), whereas the others involved many participants with controlled state of metastases and higher chronic pains. In our opinion calcitonin can be considered an effective choice to try for the patient with acute and severe pain due to malignancies along with other drugs. We gathered a summary of studies investigating the analgesic effect of calcitonin in Tables 1 and 2.

Complex regional pain syndrome

In many studies calcitonin was used commonly to treat patients with complex regional pain syndrome Type 1 (CRPS-I). However its usefulness is sometimes can be controversial.

A study conducted by Schurmann et al. on twenty four participants suffered from the CRPS-I in the upper limb investigated the effect of 0.5 mg of subcutaneous calcitonin injected daily for 8 weeks. Improvements were observed in the patients treated with calcitonin in terms of all the examined parameters, namely systematic temperature difference, hand function, edema, grip strength and spontaneous pain. However the only significant improvement was the reduction in edema. Mainly gastroenterological severe side-effects were observed in 83% of the calcitonin-treated patients. The therapy was therefore discontinued in 3 (13%) of the cases. Calcitonin therapy was found to cause only a slight therapeutic improvement and to be associated with a lot of unbearable side-effects. Authors concluded that

Table 1 Summary of studies supported the effect of calcitonin on the pain secondary to bone metastasis.

Study	Number of participants	Type of study	Participants	Intervention	Outcome
Hindley[56]	25	Prospective double-blind placebo-controlled trial	Pain secondary to bone metastases	Injections 200 IU of calcitonin at 6 hourly intervals for 48 h	Reduction in the severity of pain
Roth and Kolaric[57]	20	Double-blind, placebo controlled		Daily 100 IU injections for 28 d	Reduction in the severity of pain
Gennari[58]	7	Double-blind, placebo controlled		100 IU per day, intramuscular	Reduction in the severity of pain
Gennari[59]	33	Double-blind, placebo controlled		100 IU per day, intramuscular	Reduction in the severity of pain
Gennari and Agnusdei[60]	22	Double-blind, placebo controlled		100 IU per day	Reduction in the severity of pain
Szántó[27]	58	Uncontrolled		Injections of calcitonin 5 times	Analgesic effect was often observed when other analgesic drugs were not effective
Schiraldi[61]	36	Double-blind, placebo controlled		Infusions of calcitonin at doses of 200 IU or 400 IU per day for 6 or 3 consecutive days	Effective in relieving pain only in patients with bone metastases
Liu[62]	91	Double-blind, placebo controlled	Patients with bone pain during the anastrozole treatment of breast cancer	200 IU/day	Reduction in the severity of pain
Fraioli[63]	1	Case report	Terminal cancer patients	Subarachnoid injection at a dose of 100 IU per 70 kg	Strong analgesic effect was observed
Martinez[28]	90	Cochrane review	Pain secondary to bone metastases	100 IU administered subcutaneously	There was no evidence that calcitonin was effective in controlling complications due to bone metastases
Tsavaris[64]	45	Prospective, nonrandomized		300 IU administered intravenously daily for 5 consecutive days	Very limitedly therapeutic effects for a short period of time
Blomqvist[65]	50	Double-blind, placebo controlled		100 IU administered subcutaneously each day for 3 months)	No improvements in the consumption of analgesic drugs and bone pain

calcitonin should only be cautiously prescribed in patients with CRPS-I.[29]

In a study by Sahin et al. one group received 1500 m/day of paracetamol and the other calcitonin 200 IU daily for two months. All the participants involved in an exercise program and physical therapy. A significant recovery was observed for all the parameters in a clinical trial study in all of the participants with acute post-trauma CRPS-I of upper limbs treated with either calcitonin or paracetamol. Both group received the same physical therapy program, although the groups were not significantly different in the different parameters of recovery. This study concluded that calcitonin did not make any desirable contributions to treating acute CRPS-I patients and only a simple analgesic combined with physical therapy was found to be an efficient therapy.[30] However in the patients with hepatic impairment or for whom routine analgesics are not safe, calcitonin is a recommendable option.

The role of calcitonin in preventing CRPS was also evaluated in patients suffering from severe post-stroke hemiplegia. An approximate incidence of 8.2% was found for CRPS during the control period in all these patients. A significantly lower incidence of CRPS was found in the calcitonin group (12.5%) compared to the control group (57.1%) with minor to serious hemiplegic patients with a maximum grade of BrST III in two groups. CRPS could be prevented when calcitonin was injected four weeks after the stroke, although weak prophylactic effects were observed when calcitonin was injected 46 days after the stroke. IM calcitonin appears to suppress the emergence of post-stroke CRPS, especially when started early following the stroke.[31]

Perez conducted a systematic review of 5 articles including 280 patients, and investigated the pain-killing effects of calcitonin in CRPS. The main study of this systematic review included a controlled clinical trial by Gobelet et al. who examined the effectiveness of physical therapy and three calcitonin doses of 100 IU per day through intranasal route on 66 patients with CRPS-I randomly assigned to two balanced groups. Twenty one interventions were investigated in terms of edema, movement range, pain and working capacity after one, three and eight weeks from the beginning of treatment. Pain and physical activity scores significantly improved in the intervention group after 8 weeks.[32] The roles of co-factors, including physical therapy were however rarely explained.

Perez concluded that using salmon calcitonin might be useful in the alleviating pain in participants with CRPS Type I. He stated that the quality-weighted and unweighted analyses showed small but statistically significant results.[5] This finding however contradicts those obtained by Kingery, who believed that evidences for the effectiveness of calcitonin in pain alleviating were inconsistent.[33]

Phantom limb pain

There is a little evidence obtained from randomized clinical trials to guide the management phantom limb pain so the treatment is still challenging clinicians. Although opioids and combined tricyclic antidepressants have been conventionally and effectively used to manage phantom limb pain, growing attention is being paid to the role of calcitonin.[34]

Calcitonin was used in a case report for the relief of severe pains associated with treatment of refractory phantom limb. A pregnant woman at the age of 29 and at 8 weeks of gestation reported a severe phantom limb pain, i.e. a score of 9–10 on a ten-point pain scale of severity following an above-knee leg amputation. The pain was not relieved after 2 weeks despite using several non-opioid and opioid painkillers, including a very high dose of IV fentanyl. After administration of calcitonin slight changes were observed in her pain within the next 3 days. The patient reported a reduction in the severity and frequency of phantom limb pain episodes on the 4th post-infusion day and the symptoms of phantom limb pain were controlled over the next 48 h allowing the anesthesiologist to taper certain medication dosages, which reduced the overall narcotic consumption of the patient.[35]

Another case report of a 71 year-old man undergoing a right-side above-knee amputation described the infusion of 200 units of IV calcitonin for managing phantom limb pain. Salmon calcitonin was administered over 30 min in 5 mL of 25% albumin injection and 50 mL of 0.9% sodium chloride. The patient received three infusions over a period of 9 days. He reported slow improvement in his symptoms, with no phantom pain one year later.[36]

A placebo-controlled double-blind crossover trial used 200 units of IV calcitonin in patients who developed phantom limb pain soon after or within 7 days after surgery. Twenty-one patients with various types of amputations were enrolled in the trial and randomly assigned to receive calcitonin (infused over 20 min) or a placebo as the first infusion therapy for pain; crossover to the alternative agent occurred if the patient requested a second infusion. If a third infusion was administered, the patient received calcitonin. All patients received at least one infusion of calcitonin. After one week, 19 patients reported a $\geq$50% decrease in pain. Follow-up extended for 2 years after the end of treatment, at which time (71.4%) of the patients reported complete amelioration of phantom limb pain. Of those patients who did not have complete pain relief at the 2 year follow-up, all reported a noticeable decrease in either the frequency or the severity of pain episodes.[37]

However, Eichenberger et al. investigated the use of calcitonin and ketamine, alone or in combination, in participants with chronic phantom limb pain. Of the 19 treated patients, 60% of those received ketamine alone, compared with only 10% of those who received calcitonin alone or in combination with ketamine, reported a reduction in pain intensity of $\geq$5. The investigators concluded that ketamine alone was superior to calcitonin alone or in combination with ketamine for the management of phantom limb pain. The analgesic impacts of a combination of ketamine and calcitonin caused significant increases in electrical thresholds, although no changes were observed in pressure and heat thresholds.[38]

These outcomes highlighted the impact of N-methyl-d-aspartate antagonists and questioned the usefulness of calcitonin for treatment of chronic pain in phantom limb. Sensory evaluations suggested that peripheral sensory system is unlikely to involve in of phantom limb pain. Therefore ketamine rather than calcitonin influences the central nervous processes that potentially contribute to the pathophysiology of phantom limb pain.[38]

However in a case report and systematic review by Viana a case of refractory phantom limb pain in a 72 year-old male due to amputation of transradial and concomitant heterotopic ossification was presented.[34] The patient was successfully treated by 4 week regime of intranasal medication of calcitonin and patient remained disease free for at least 18 months. Also 17 articles were included in their review and 11 of them were randomized controlled trials. However all studies had limited sample size and short follow-up period. They concluded that most of the studies supported calcitonin administration were those with limited study follow-ups (hours to days).[34]

These studies emphasize that calcitonin is convenient and easily tolerated and may be good option for severe and acute pain (not chronic)[38] in patients where other pain medications are contraindicated or fail to help and also in the case of treatment-resistant phantom limb pain.

Syndromes

McCune-Albright syndrome

In a case report, a 27 year-old female diagnosed with McCune-Albright Syndrome at the age of 4 years was presented. The patient suffered from multiple fractures and treatment-resistance bone pain to alendronate, amitriptyline and opioids which rendered the patient incapacitated to wheelchair. Nasal spray of calcitonin (200 IU BID) for 30 days improved the severity of the bone pain and after 3 months, she was able to walk without assistance. Again this case insisted on the usefulness of calcitonin for short-term treatment of refractory and severe bone pain.[12]

Camurati-Engelmann disease

Camurati-Engelmann disease is inherited with autosomal dominant pattern and characterized by thickening and bilateral sclerosis of long bones. Bone pain is one of the common symptoms. In this case pain management was performed using NSAIDs from the age of 8 to age 24 years in the male patient with Camurati-Engelmann. Then at the age of 25, medications changed to 1375 mg of naproxen and 500 mg of aspirin, and the results showed a variable response.[39] The physicians decided to add 200 IU daily nasal spray of salmon calcitonin and then the pain intensity decreased steadily which leaded to a state of optimum pain control after 3 months. One month after using calcitonin, patient stopped taking the naproxen. After 3 months the VAS pain score of 0 was achieved in the morning and the score 1 during nights using 250 mg of aspirin.[39]

Spinal cord injury mediated neuropathic pain

Complex neural mechanisms contribute to neuropathic pains that are caused by spinal cord injuries and are often refractory to standard therapy. In a series of case reports on 3 patients with recent injuries to the spinal cord, Humble found salmon calcitonin to be an effective treatment in neuropathic symptoms.[40]

Atypical facial pain

Schwarts et al. investigated the pain-relieving features of salmon calcitonin for treating atypical facial pain. Salmon calcitonin 100 IU per 1 mL of saline was used in an open-label manner in thirteen patients with refractory atypical facial pain for 6 weeks, five times a week. The study was halted due to the high drop-out rate of the patients (57%). No differences were observed in the outcome measures in the patients receiving either placebo or active drug and a high emergence of side effects caused a dropout in the patient receiving calcitonin. Despite its analgesic properties, salmon calcitonin was found not to affect atypical facial pain, mainly owing to its side effects.[41] However we believe that further studies using calcitonin administrated nasally which can help reduce unpleasant side effects should be conducted to achieve more reliable results.

Painful diabetic neuropathy

The painkilling role of salmon calcitonin nasal spray was showed by Zieleniewski in a female patient with painful diabetic neuropathy.[42]

Quatrato also used this substance in 10 insulin-treated diabetics. All of the participants were suffered from neuropathic pain in leg, and their vibratory level of perception was over the normal age-adjusted upper limit. Analgesics and NSAIDs medications used to treat the patients resulted in poor outcomes. Before entering the study, the patients discontinued the neuropathy treatment, and warned to avoid taking aspirin and other analgesics during the whole study period. Based on a randomized double-blind procedure, these ten diabetics were then given 100 IU of calcitonin nasal spray daily as well as placebo. The salmon calcitonin treatment and placebo administration continued for 2 weeks and were suspended for a 2 week as wash-out period. The participants who received calcitonin first were given the placebo later and vice versa. The participants rated their degree of neuropathic symptoms, i.e. tenderness, deep ache and burning, on a VAS graded between 0 and 10, with 0 denoting no symptoms and 10 very severe. Three participants completely relieved from the symptoms and a 50% improvement was observed in another patient. Calcitonin is a recommendable medication if the other analgesics fail to control the pain on the basis of the facts that a minimum 30% of participants reported that their symptoms almost gone and that the medication was safe, easy to administer and did not adversely interfere with the carbohydrate metabolism.[43]

Herpetic neuropathy

A report presented by Visser et al. involved a 78 year-old male patient with post-herpetic related neuralgia who received amitryptyline, carbamazepin, narcotics and traditional painkillers which had failed mainly owing to side effects, especially nausea, dizziness and sedation. Given calcitonin effectiveness in treating neuropathic pain syndromes and relatively low profile adverse effects, IV salmon calcitonin was then administered. Over 2 months of follow-up, participant reported sustained immediate improvements

in the herpetic related neuralgia, without adverse effects associated with medication.[44]

Calcitonin versus diclofenac for the treatment of low back pain

Zhou compared the effect of diclofenac sodium and calcitonin on treating patients with Type I Modic changes and nonspecific Low Back Pain (LBP). This retrospective observational study was performed on 109 patients with nonspecific low back pain and Type I Modic changes appearing as bone marrow involvement on MRI. Sixty two patients were intramuscularly injected with 50 IU of calcitonin once a day and 47 patients were given 75 mg of diclofenac once a day for 4 weeks. The results suggested significant changes in VAS compared to the baseline in both groups in follow-ups. Also the higher proportion of patients receiving the calcitonin experience more significant improvement in LBP scales. MRI results showed improvements in 43.54% of the calcitonin group vs. 21.27% in the diclofenac group. According to MRI results, calcitonin caused superior improvement in short-term effect compared with diclofenac in patients with Type I Modic changes and LBP.[2]

However Papadokostakis in a clinical trial on 110 women with chronic back pain due to fractures or degenerative conditions showed that 200 IU of intranasal calcitonin was an ineffective treatment for chronic back pain and improving functional ability of osteoporotic female.[45] On the other hand, Ofluoglu used 100 IU of subcutaneous calcitonin to treat the back pain in 30 female patients with osteoporosis. The group receiving calcitonin showed significant improvement in pain and functional scores. Also results showed that calcitonin increased the beta-endorphin levels significantly at the end of the second week.[46]

Postoperative pain control

A study compared the analgesic effects of the epidural administration of opioids with salmon calcitonin on the postoperative pain. This prospective study was conducted on 53 patients with ASA I–II scheduled for a complete hip arthoplasty under epidural anesthesia. These participants were assigned to three groups randomly, each receiving a mixture of 10 mL different solutions to control postoperative pains. Group A received 3 mL of NaCl 0.9%, 2 mL of fentanyl 100 mcg and 5 mL of bupivacaine 0.5%. Also 4 mL of NaCl 0.9%, 1 mL of salmon calcitonin 100 IU and 5 mL of bupivacaine 0.5% were administered in Group B. Finally, Group C received 9 mL of NaCl 0.9% and 1 mL of salmon calcitonin 100 IU. Epidural salmon calcitonin combined with local anesthetic was found to cause analgesic effects with stable hemodynamic results similar to fentanyl. Calcitonin was also able to eliminate postoperative hyperglycaemia. The plasma levels of cortisol did not increase during the first hour after operation, although it increased noticeably during the next hour. This study found calcitonin to be an appropriate alternative for treating acute postoperative pains.[10]

Maxillofacial surgery

In a case report of a 57 year-old female with symptoms of paraesthesia of the lip, pain, discharging of pus from sinus track in the submandibular region and mandibular fracture, calcitonin was used to treat the pain. The patient developed these symptoms three months after extraction of third molar which were suggestive of chronic osteomyelitis. Radiographic investigations demonstrated destruction of the cortical bone plate in the body and angle of mandible to the inferior border and subsequent mandibular fracture. The patient was prescribed with subcutaneous salmon calcitonin 50 units/daily which considerably relieved the bone pain and improved bone healing. The patient was discharged with metronidazole, cefradine and continuing calcitonin for 7 month.[47]

Also in a study on the 46 patients with maxillofacial fracture, the effect calcitonin on the pain intensity and analgesic consumption after surgery was investigated in a 7 day follow-up. Intervention group received 200 unit of calcitonin nasal spray after surgery and the control group received normal saline serum nasal spray. The results showed that the pain intensity between two groups was not significant however in the 6th and 7th day the total acetaminophen consumption was significantly lower in the intervention group. This result again showed that calcitonin might be a useful medication to help to control the postoperative pain by reducing the required dose of routine painkillers.[48]

Trigeminal neuralgia

The first line treatment to manage the trigeminal neuralgia is pharmacotherapy. However a high number of patients become refractory to the routine medications. A randomized double-blind clinical trial by Elskeikh used a modified coronoid approach to investigate the impact of a combination of calcitonin and lidocaine *vs*. methylprednisolone on managing trigeminal neuralgia pains involving maxillary and mandibular branches.

Group 1 received a block injection of 40 mg of methylprednisolone, 3 mL of lidocaine 0.5% and a syringe with 1 mL of 0.9% saline. Group 2 received a block of 40 mg of methylprednisolone, 3 mL of lidocaine 0.5% and a syringe with 50 IU of calcitonin.

Effective pain relief was found to be significantly longer in Group 2 compared to Group 1. Repeated blocks were not needed in four patients in the first group versus fifteen in the second group. No critical side effects were experienced during or after the intervention. The VAS score was found to be comparable in both the groups ($p > 0.05$). Trigeminal neuralgia can therefore be well managed using calcitonin as an additive to steroid and local anesthetic.[11] Studies investigating the possible pathophysiology of trigeminal neuralgia showed an increased level of Calcitonin Gene-Related Peptide (CGRP) and decreased level of beta-endorphin in cerebrospinal fluid.[49] And the medication which can reverse the increased expression of CGRP and c-Fos in spinal trigeminal nucleus also can alleviate the trigeminal neuralgic pain.[50] Considering the fact that calcitonin can also decreased the increased expression of CGRP and c-Fos in dura[1] and also the possible relation of calcitonin with

increased plasma level of beta endorphin[46] we can explain the effect of calcitonin in trigeminal neuralgia treatment.

Migraine

We also reviewed the studies that investigated the role of calcitonin in management and prevention of migraine.[1,16,51]

Kilink showed that salmon calcitonin can relieve migraine-like pain through modulating the release of calcitonin gene-related peptide, and stabilizing the mast cell activities in the dura mater. Therefore salmon calcitonin can be considered an alternative treatment for relieving migraine pains.[1]

Micielialso evaluated the activity and studied the pharmacological profile of a nasal spray of salmon calcitonin in patients with migraine. A clinical trial was conducted on 22 patients with common migraine. From the first month of the therapy, salmon calcitonin (200 UI at bed time) was found to significantly reduce analgesic consumption, the total pain index and the headache index. The results demonstrated the role of administrating nasal calcitonin in migraine management, and outlined a complex pharmacological profile for salmon calcitonin, ranging from analgesic activities to the modifying of the neurons and neuro-transmitter release triggering migraine headache.[16]

Moreover, Ustdal investigated the effects of a 5 day IM treatment with calcitonin 100 IU on the plasma levels of corticosteroids, beta endorphin and ACTH in twenty participants with migraine when they were free of headache. Before and after the calcitonin treatment, significant statistical correlations were observed among ACTH, β- endorphin and cortisol levels. Calcitonin administration increased all the three hormones and the maximum increase was found in the levels of β-endorphin.[51]

Adverse effects and safety

Salmon calcitonin is believed to be very safe, in several studies and in the post-marketing period more than 30 years and with several million patients using it every year.[52] The main contraindication is hypersensitivity to components of calcitonin. So before systemic administration of this drug if hypersensitivity is suspected, patient can benefit from skin testing.[52] Systemic adverse effects, including flush or nausea are more common with the parenteral or intramuscular administration than the nasal spray form.[18,29,41,45] In clinical trials, frequency of adverse event were generally comparable between calcitonin and control group. For calcitonin, the patients frequently reported transient local involvements likes tingling of the nasal route, rhinitis, sneezing and nasal mucosal irritation. Of these adverse effects, 97% were considered mild to moderate, and up to 10% of patients receiving calcitonin experience these side effects.[9,18] Overall, calcitonin compares favorably versus other analgesic drugs in terms of adverse effects, precautions, interactions with other treatments and contraindications.[2,20,35] Because of the transient not permanent suppression of osteoclasts and according to longstanding clinical trials, it seems that there are to no potential for detrimental effects on skeletal system and other organs during long-term medication.[28]

Discussion

This study accesses all the possible uses of calcitonin for pain management. To do so, we performed a meticulous and thorough search on online databases including MEDLINE, Scopus, Google scholar and Cochrane library using the key search terms ''pain, analgesic and calcitonin''. Then we evaluated all eligible articles to investigate the analgesic efficacy of calcitonin for different painful states.

Standard pain therapies including opioids, NSAIDs and acetaminophen are usually effective to manage pain especially nociceptive types with different intensities ranging from mild to moderate and even severe.[53,54] These agents however pose risks such as psychological adverse effects, hepatic gastrointestinal and renal or interactions with different medications like bisphosphonates and different antihypertensives. Calcitonin is considered an effective analgesic in many patients unable of tolerating NSAIDs drugs and narcotics. Whether or not calcitonin is superior to commonly prescribed analgesics is yet to be investigated more. However one study showed its superiority to diclofenac in treating patients with nonspecific LBP and another study showed that it was more effective than gabapentin in management of lumbar canal stenosis radiating pain.[2,20] In the current review we showed that calcitonin had analgesic effect on several painful circumstances including nociceptive pains (either somatic or visceral) and neuropathic pains. Nociceptive pains (somatic type) which were investigated in this review included acute and chronic pains related to vertebral fractures, lumbar canal stenosis, radius fracture, atypical facial pain and visceral type including pain due to metastasis and migraine. Also neuropathic pains included in our list are the painful diabetic neuropathy, reflex sympathetic dystrophy, neuropathic pains related to spinal injuries, herpetic neuralgic pain and phantom pain. Also calcitonin was investigated as an additive to local anesthesia more effective treatment of postoperative pain or trigeminal neuralgia. Gathered data show some contradictory results for conditions like lumbar canal stenosis, complex regional pain syndrome, phantom pain and malignancies. Finally after evaluating these data we showed that calcitonin was a feasible alternative for the short-term treatment of the pain related to acute vertebral fractures and when a long list of medicines proposed for different distressing condition such as phantom limb pain, neuropathies, CRPS, pain due to malignancies and several other acute and chronic painful conditions were still unsatisfactory. It is interesting to note that in a Cochrane study, despite of the analgesic effect of anticonvulsant drugs on the chronic pains, they had no positive effect on the treatment of acute pain.[55] However calcitonin is effective on both acute and chronic pain. The possible reason is the broad involvement of calcitonin in many pathways controlling pain which explained in mechanisms subsection.

Several reasons can be proposed for why calcitonin should be used when usual analgesics fail control pain. Firstly, according to the review by the authors, patients can experience near-complete relief of symptoms in many painful circumstances, especially in acute pain and neuropathies. Secondly, the drug is safe, simple to administer and does not cause significant adverse effects on different metabolism

pathways. Thirdly, calcitonin can be useful medications for whom with renal, liver and intestinal problems to reduce the required dose of analgesics. However in healthy patients this advantage is less prominent due to economical factor, possibility of reduced patient compliance due to a longer list of prescribed drugs and finally meager benefits for healthy patients.[30]

Conclusion

After evaluation of these studies investigating the effect of calcitonin on nociceptive (either somatic or visceral) and neuropathic pains, we concluded that calcitonin could be considered as eligible treatment for acute pains related to vertebral fractures and a feasible alternative for the treatment of the acute and chronic neuropathic pains due to diabetes, herpetic conditions and spinal cord injuries, migraine, phantom pains and CRPS I where the other analgesic agents failed. But in the chronic pain related to vertebral fractures and malignancies calcitonin seemed to be less effective. Also calcitonin was showed to be a useful additive to local anesthesia in the case of controlling postoperative pain or trigeminal neuralgia. Finally, for further investigations, we suggest to study the possible mechanism for the peripheral and central effect of calcitonin in treatment of trigeminal neuralgia. Also the effectiveness nasal spray of calcitonin in treatment of facial pains can be investigated. More studies with more robust design with sufficient participants and follow-up period are necessary to investigate the clinical efficacy of calcitonin in different neuropathic situations. As the final word, the better we understand the molecular mechanism and physiology of calcitonin as an analgesic agent, the better we can administer it in clinical situations and more effective painkillers with lower side effects will possibly be introduced in future.

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Conflicts of interest

The authors declare no conflicts of interest.

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