Reviews

Calcitonin (FORTICAL, MIACALCIN) for the treatment of vertebral compression fractures

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Purpose of Review

Osteoporosis is a common condition affecting the musculoskeletal system. It carries with it increased risks of fracture in many areas of the body, leading to reduced quality of life, limited mobility, and other long-term implications such as chronic pain. Vertebral compression fractures are a common development in patients with osteoporosis. Current treatment options focus on reducing pain; preventative methods are somewhat limited and focus on minimizing risk factors for the development of osteoporosis. In this review, we explore the use of calcitonin (FORTICAL, MIACALCIN) to treat vertebral compression fractures (VCFs).

Recent Findings

Osteoporosis had a prevalence of more than 10% in the United States in 2010. The CDC estimates that nearly 25% of women over age 65 have findings of osteoporosis, which include low spinal bone mass. The condition is highly prevalent and, in an aging U.S. population, quite clinically relevant. Risk factors for development include advanced age, cigarette smoking, medications, reduced physical activity, and low calcium and vitamin D intake. Family history may also play a role. Diagnosis is made based on bone mineral density.

Standard therapy for VCFs in osteoporosis includes analgesic medications, such as NSAIDs and biphosphonates, and surgical intervention. NSAIDs address the chronic pain that is a common long-term effect of VCFs. Biphosphonates have recently been used to attempt to halt the progression and provide prevention. Surgical interventions such as balloon kyphoplasty and vertebroplasty are typically reserved for patients who have failed other methods.

Calcitonin is a peptide naturally produced by the human body, released from the parathyroid gland. It binds to osteoclasts, inhibiting them from inducing bone resorption. By relatively unknown mechanisms, it also appears to cause endorphin release and mitigate pain. Clinical data has shown safety and efficacy for exogenous calcitonin in reducing bone turnover and reducing VCF-induced pain.

Summary

Osteoporosis is a common condition that can lead to complications such as vertebral compression fractures. It can significantly impact the quality of life in many elderly Americans. There is currently no singular treatment, but calcitonin has recently been explored as a possible option for minimizing pain and reducing disease progression. Further studies are needed to understand its preventative benefits fully.

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INTRODUCTION

Osteoporosis is a disorder characterized by decreased bone strength that predisposes individuals to fractures of the spine, hip, and other sites. The condition had a prevalence of more than 10% in the United States in 2010, and the CDC estimates that nearly 25% of women over age 65 have findings of osteoporosis.¹ There are many risk factors associated with osteoporotic fractures, including older age, cigarette smoking, use of certain drugs (e.g., corticosteroids), low peak bone mass, low physical activity, and low vitamin D and calcium intake hormonal factors, and personal or family history.² Vertebral compression fractures (VCFs) are a hallmark and common sequela of osteoporosis, representing one of the most common types of fragility fractures with an annual incidence of up to 1.4 million.^{3–6} They affect about 25% of postmenopausal women overall, and the prevalence increases with age, reaching 40% in women 80 years old.^{3,7–9} Acute fractures occur when the vertebral body cannot support the load of the upper body; with severe cases of osteoporosis, inciting incidents can be minor (e.g., vigorous sneezing or stepping out of a bathtub). More force is required in cases of moderate osteoporosis (e.g., attempting to lift a heavy object or falling out of a chair). The majority of damage is generally within the anterior vertebral column; therefore, the fracture is typically stable and rarely causes neurologic compromise.^{3,10} However, multiple fractures can result in significant loss of height through thoracic kyphosis and lumbar lordosis while shortening paraspinal musculature, requiring active contraction to maintain posture and subsequently causing pain from muscle fatigue.^{3,11} In addition to causing pain, VCFs increase the risk of secondary fractures 4-fold, impede respiratory function, and increase overall mortality risk.^{6,12–14} Conservative treatment is nonoperative and includes physical therapy and pain control with analgesics, while more interventional procedures (e.g., vertebroplasty, kyphoplasty) are considered in those who are unresponsive to conservative treatment.^{3,4} Meanwhile, adequate diagnosis and treatment of osteoporosis itself reduces the incidence of VCFs.^{3,15–17}

CURRENT/TRADITIONAL TREATMENT

Treatment goals of VCFs aim to restore mobility, reduce pain, and reduce the risk of further fractures. Initial treatment should be conservative, using the World Health Organization pain ladder to guide analgesic treatment. Additionally, early mobilization should be encouraged as tolerated in stable fractures.⁴ A meta-analysis demonstrated that spinal orthoses might have value for short-term pain relief and disability; however, the claims are limited by low-quality evidence.¹⁸ While orthoses may be temporarily helpful. There is little evidence to support their ability to achieve definitive stabilization or have significant long-term efficacy.^{4,19} In most patients, the pain will significantly decrease in the first six months of conservative management. However, a third of patients will still have severe pain requiring physical therapy and oral analgesia two years after an acute fracture.^{4,20} A retrospective study of patients

with acute osteoporotic VCFs showed that risk factors for conservative treatment failure include: age > 73.5 years, body mass index > 23.65, bone mineral density < -3.45, and a modified frailty index > 2.5.⁵ In these groups of patients, a more invasive approach may be pursued.

Patients with acute fractures, ongoing pain despite optimal pain management, and edema within the vertebral body on magnetic resonance imaging (MRI) could be candidates for balloon kyphoplasty. This minimally invasive procedure aims to relieve pain, prevent further collapse, and reduce the kyphotic deformity. A balloon-like device is inserted with radiographic guidance in this procedure and is inflated to restore vertebral height. After which, it is deflated, and the air-filled space is injected with bone cement.^{4,21} Conversely, vertebroplasty is another minimally invasive procedure that involves injecting bone cement into the vertebral body directly without balloon inflation. Both kyphoplasty and vertebroplasty are widely used depending on local expertise and availability.⁴ Compared to conservative treatment methods, these procedures have demonstrated fewer subsequent fractures, increased survival, better pain relief, and a favorable cost-effectiveness profile.^{22–25} A meta-analysis comparing the two reported no difference in short- and long-term pain and disability scores.^{4,26} Adverse effects of these procedures include bleeding, infection, systemic reactions, neurologic damage from needle insertion, and cement leakage (9% in kyphoplasty and as much as 41% in vertebroplasty).^{4,27} Since there is no balloon with vertebroplasty, the cement must be injected at a higher pressure, which is why it increases the risk of cement leakage.^{4,28} However, with kyphoplasty, there is a small risk that the balloon can rupture, leaving its fragments within the vertebral body.⁴ As both of these techniques have their adverse event risks. They are typically utilized after conservative treatment failure. However, the optimal timing for these procedures remains controversial. While there are risks for adverse events, early intervention may prevent further vertebral collapse, allowing for prompt mobilization.^{4,29}

Unstable VCFs include those involving the posterior column ligamentous or bony structures or burst fractures with significant fragment retropulsion, more than 50% loss of vertebral height, and over 25–35 degrees of kyphosis. These fractures often require open surgical stabilization.⁴ This relieves pain by reducing movement and further displacement at the fracture site, effectively preventing potential spinal cord or nerve root compromise. If there is evidence of neurological deficit, this is often coupled with local decompression.⁴

Approximately 20% of patients with symptomatic VCFs can be expected to develop chronic pain.^{4,30} These patients may benefit from a multidisciplinary pain team. Alternative therapies such as transcutaneous electrical nerve stimulation, acupuncture, and cognitive behavioral therapy can help improve quality of life. Furthermore, treatment of underlying osteoporosis is essential to prevent secondary fractures. This includes lifestyle modifications such as smoking cessation, decreasing alcohol intake, and supplementary calcium and vitamin D.⁴ Osteoporosis medications can also be used to prevent the occurrence of VCFs. A meta-analysis found bisphosphonates (zoledronate, risedronate, alen-

dronate, ibandronate, minodronate, etidronate, and pamidronate), parathyroid hormone, denosumab, romosozumab, and selective estrogen receptor modulators (SERMs) to have significant prevention effects for VCFs.¹⁴ The proven protective effects of these medications consider the potential impact of another osteoporosis medication, calcitonin.

CALCITONIN DRUG/PRESCRIBING INFO

With various calcitonin products on the market, it is essential to consider the prescribing information of the different forms. Calcitonin was traditionally administered parenterally and intranasally, but oral administration may lead to higher compliance with calcitonin therapy. In healthy volunteers, FORTICAL calcitonin-salmon is rapidly absorbed by the nasal mucosa. Additionally, there is no accumulation of the nasal spray when administered at 10-hour intervals for 15 days.³¹ FORTICAL salmon calcitonin has been indicated in postmenopausal women (greater than five years post-menopause) combined with daily consumption of calcium and Vitamin D (at least 1000 mg elemental calcium per day 400 international units per day, respectively). MIACALCIN nasal spray has been shown not to increase bone mineral density.³¹ MIACALCIN is indicated for intranasal use only. Before use, individuals should ensure adequate calcium and vitamin D levels, allow the bottle to reach room temperature, and prime the pump. Once this has been completed, 200 IU/day should be administered daily to alternating nostrils.³²

For both FORTICAL and MIACALCIN, given suspected sensitivity, skin testing should be considered. Allergic reactions have been reported toward the preservative present in the nasal spray rather than to calcitonin itself. While no formal contraindications have been assessed, reports state that prior use of diphosphonate to treat Paget's disease can decrease the anti-resorptive properties of the nasal spray. Due to the possibility of rhinitis, epistaxis, and sinusitis, it is recommended that periodic nasal examinations are performed.³¹

CALCITONIN ORIGINAL USE

In the 1960s, the discovery of a 32-amino acid peptide, calcitonin, was made. Calcitonin was found to be released from the parathyroid gland and inhibited osteoclast activity in response to increased serum calcium levels.³³ This endogenous polypeptide plays an essential role in both calcium homeostasis and bone remodeling.³⁴ Calcitonin's original use was to treat bone disorders and mineral metabolism by inhibiting the bone resorptive activity of osteoclasts.³⁵ Calcitonin does this by internalizing the ruffle proteins of osteoclasts, preventing their release of acid, and preserving the bone matrix.³⁶ Additionally, it was discovered that calcitonin acts upon the kidneys to reduce the reabsorption of calcium, chloride, sodium, potassium, and phosphate and works on the central nervous system to induce analgesia.³⁶

With the endogenous effects of calcitonin on the body discovered, scientists worked to find additional uses for calcitonin as a form of treatment. The original study results on

the efficacy of injectable calcitonin, Calcimar, were somewhat contested, as it was unclear whether the drug increased bone mineral content. After nearly thirty years after the initial discovery, a nasal spray form of calcitonin, Miacalcin, received FDA approval to treat postmenopausal osteoporosis and later showed evidence to reduce bone fractures.³⁶

In addition, to treat postmenopausal osteoporosis, calcitonin possesses analgesic properties that warrant its use in pain management for recent vertebral fracture injuries.³⁶ The analgesic properties of calcitonin have been found to reduce pain and increase mobility and maintain the quality of life in its users.³⁷ Other injectable forms of calcitonin were on the market but quickly replaced by the nasal form due to the injectables' extensive side effects, such as nausea and vomiting.³⁶

Before the discovery of bisphosphonates, calcitonin was the first effective drug to treat Paget's disease by reducing bone turnover, relieving osteogenic pain, and healing disease-induced lesions.³⁵ Calcitonin is currently approved to treat diseases involving accelerated bone turnover. These include osteoporosis, malignancy-associated hypercalcemia, and Paget's disease.³⁸

MECHANISM OF ACTION

Endogenous calcitonin acts by directly binding to receptor sites on the surface of osteoclasts.³⁹ This causes reversible changes to the cytoskeleton of osteoclasts, which leads to a decrease in binding to mineralized bone surfaces and bone resorption.³⁹ The mechanism of exogenous calcitonin is not as clear. Despite exogenous calcitonin's known effect as an analgesic, multiple hypotheses have been presented explaining this effect. One observation noted that the intravenous administration of salmon calcitonin in humans led to increased plasma beta-endorphin levels. While calcitonin has been compared to the endorphin-releasing effects produced by morphine, an experiment by Yamazaki et al. demonstrated that the opioid receptor antagonist, naloxone, inhibits the antinociceptive actions of morphine, but not that of eel calcitonin. This suggests that the mechanism of action of calcitonin is distinct from opioidergic systems.⁴⁰ Yamazaki and his team found that the antinociceptive action of eel calcitonin was inhibited by the serotonin-receptor antagonists, suggesting that a serotonergic mechanism is at play.⁴⁰ Further support for the serotonergic terminals is shown via experiments where 5,7 DHT is injected into the dorsal raphe, blocking the effects of salmon calcitonin when injected intracerebroventricularly.⁴¹ Experiments conducted by Ito and Yoshimura on ovariectomized rats demonstrate that calcitonin may decrease neuronal hyperexcitability by restoring 5-HT receptors and normalizing voltage-dependent sodium channels anti-hyperalgesic effect.³⁸ Another potential explanation poses the possibility of anti-inflammatory properties of calcitonin by blocking prostaglandin E2 synthesis.⁴² Experiments on guinea pig lungs perfused with arachidonic acid were treated with calcitonin resulting in a 50% decrease in arachidonic acid and thus a reduction in the prostaglandin system.⁴² Others hypothesize that there may be an internalization of calcitonin receptors, decreasing the amount of

readily available surface receptors.³¹ Yet others explore potential mechanisms that may occur centrally (8). An experiment conducted by Pecile in 1975 demonstrated that intracerebroventricular injections of salmon calcitonin in rabbits dramatically increased the pain threshold.⁴³ Thus, it is hypothesized that calcitonin may pass the blood-brain barrier, accumulating and stimulating calcitonin receptors in various brain locations. In rats, one such location was found pons-medulla.⁴⁴ In humans, salmon calcitonin was injected into the subarachnoid and demonstrated long-lasting effects.³⁷

PHARMACOKINETICS/PHARMACODYNAMICS

PHARMACODYNAMICS

Studies have shown that specific biochemical markers may be representative of the pharmacodynamics of salmon calcitonin.⁴⁵ In terms of oral calcitonin, the C-terminal telopeptide of type 1 (CTX-1) and type 2 collagen (CTX-2) are accurate bone and cartilage degradation markers, respectively. As a marker for bone resorption, serum CTX-1 levels decreased by 80% when given a dose of salmon calcitonin to postmenopausal women.³⁸ Additionally, salmon calcitonin decreased urine CTX-2 by 60% in postmenopausal women for both recombinant and synthetic salmon calcitonin.³⁸ Compared to mammalian calcitonin, salmon calcitonin has the most significant biological activity, undergoes the least amount of degradation by serum factors, has the longest half-life, and shows the highest affinity for receptors in bones and kidneys.³³ After intravenous administration of 1, 5 and 10 µg, salmon calcitonin has followed linear pharmacokinetics.³³ Studies using a 0.8 mg dose of salmon calcitonin showed that the time to maximum concentration is 15 minutes, and the half-life is between 9 to 15 minutes.³¹ The AUC for salmon calcitonin (0.8 mg dose) is ten times greater than 200 units of intranasally administered salmon calcitonin, indicating that oral routes of administration are more readily absorbed. The efficacy of salmon calcitonin is observed at 30ng/kg and demonstrates a rebound effect at 300ng/kg as it reaches basal levels.⁴⁶ In preventing retinoid-induced hypercalcemia, salmon calcitonin is effective at 5IU/kg or greater and shows an ED50 of 3.0IU/kg.⁴⁶ While there have been limited studies of the hepatic metabolism of salmon calcitonin in humans, studies on rats and intestinal vascular access port (IVAP) dogs provide useful information on the drug's pharmacokinetics. Studies conclude that hepatic metabolism of salmon calcitonin is minimal, and entry into the portal vein is the rate-limiting step to successful oral administration of salmon calcitonin.³⁴

IMPROVING BIOAVAILABILITY

To increase the permeability of salmon calcitonin across the G.I. wall, pegylation, glycosylation, and lipidization have been found to increase the bioavailability of the drug.⁴⁷ Additionally, factors such as water intake, food intake, and time of oral administration have been shown to affect the pharmacodynamics of oral salmon calcitonin.³¹ Food intake affects gastric emptying time, where less water ingested minutes after oral administration can increase the AUC and

greater reduction of bone resorption. Taking a tablet 10 minutes before a meal can significantly maximize salmon calcitonin bioavailability and better outcomes for decreasing bone resorption.³¹ Studies conducted on postmenopausal women demonstrated that the greatest efficacy of oral calcitonin occurred in the evening.⁴⁸

CLINICAL STUDIES: SAFETY AND EFFICACY

Calcitonin is a pharmaceutical option that may be employed acutely after an osteoporotic fracture or for patients with postural irregularities. It offers early mitigation of pain and enhanced quality of life while posing few unfavorable severe side effects.⁴⁹ To address the efficacy of calcitonin from treatment vertebral compression fractures, one double-blind and randomized controlled trial studied 565 postmenopausal osteoporotic women aged 46 to 86. Participants were placed into a total of 3 groups.⁵⁰ All women received supplemental calcium (≥ 1000 mg/d) and vitamin D (800 IU/d) but were further subdivided into three groups to receive: oral recombinant salmon calcitonin tablets (rsCT) (.2mg/d) plus placebo nasal spray; synthetic salmon calcitonin nasal spray (ssCT) (200 IU/d) plus placebo tablets; or only placebo (placebo tablets plus placebo nasal spray); for 48 weeks.⁵⁰ The results demonstrated that the women receiving the oral rsCT and ssCT had a significant increase from baseline in lumbar spine bone mineral density (BMD) of $(1.5\% \pm 3.2\%)$ and $(0.78\% \pm 2.9\%)$ respectively, while no change was observed in the placebo group $(0.5\% \pm 3.2\%)$.⁵⁰

In addition to its positive effects on lumbar spine BMD, oral rsCT was found to be both non-inferior and superior ($P=.027$) to the ssCT, and the difference between the oral rsCT and placebo group was significant ($P=.010$).⁵⁰ However, there was no difference in the lumbar spine BMD between the ssCT and placebo groups.⁵⁰ Additionally, the oral rsCT group showed an increase from baseline in trochanteric $(0.64\% \pm 3.09\%)$ ($p < 0.001$) and femoral neck $(0.33\% \pm 3.44\%)$ ($p = 0.057$) BMD with the total hip BMD not significantly changed $(-0.23\% \pm 2.18\%)$.⁵⁰ Both the ssCT group and the placebo group showed no significant changes in the BMD of the trochanter and femoral neck, but there was conversely a noted decrease in BMD in the total hip area.⁵⁰ Reductions in two bone resorption markers (cross-linked C-telopeptide 1 [CTX-1] ($p < 0.001$) and total amino-terminal propeptide of type I procollagen [P1NP]) ($p \frac{1}{4} 0.033$), were found to be significant between the oral rsCT group and the ssCT, and the difference between all three markers was (cross-linked C-telopeptide 1 [CTX-1] ($p \frac{1}{4} 0.001$), cross-linked N-telopeptide of type I collagen 1 [NTx-1] ($p \frac{1}{4} 0.009$), and total amino-terminal propeptide of type I procollagen [P1NP] ($p \frac{1}{4} 0.001$)) significant when the oral rsCT and placebo groups were compared.⁵⁰

Another study aimed to directly quantify the number of postmenopausal women with a new vertebral fracture in a 36 month-long randomized controlled trial.⁵¹ 3310 postmenopausal osteoporotic women were randomly assigned to receive oral salmon calcitonin (0.8 mg/d) or placebo, with both groups also receiving calcium and vitamin D.⁵¹ It was therefore concluded that there was no difference in the number of new vertebral fractures or risk of a new vertebral fracture between the oral calcitonin (3.21% experienced

new fractures) or placebo group (3.52% experienced new fractures). However, there were fewer hip fractures and a significantly longer time to first hip fracture noted in the oral calcitonin group (incidence = .1% per patient-year exposure) compared to the placebo group (incidence = .7% per patient-year exposure).⁵¹ A small increase in BMD of the femoral neck and hip was observed in both groups and a 1.02% increase in BMD of the lumbar spine in the oral calcitonin group compared to the .18% increase found in the placebo group ($p < 0.0001$).⁵¹ Additionally, significantly fewer bone metabolism biomarkers were found in the urine of the oral calcitonin subjects compared to the placebo subjects at 12 and 24 months only, but this did not correlate to any significant difference in pain score or quality of life (assessed by the Qualeffo-14 questionnaire) between the groups.⁵¹

Calcitonin can be administered in routes other than oral or nasal. Calcitonin suppositories (200 IU) used as an analgesic therapy in patients with a recent non-traumatic osteoporotic vertebral crush fracture were utilized for 28 days in a prospective clinical trial to compare this calcitonin therapy to paracetamol tablets (500mg) plus bed rest in 40 patients.⁵² There was a statistically significant decrease in spinal pain assessed by the Huskisson's visual analog scale (VAS) and a pain-meter device, which led to early mobilization, sitting, standing, walking, and significantly less bone turnover in the calcitonin suppository group.⁵² All patients in the calcitonin group were able to sit by the end of the second week and walk by the third week, while only four of the placebo group patients could sit at the end of the study, and none were able to walk.⁵² To directly analyze the role of calcitonin as a treatment for acute and chronic pain, a systematic review and meta-analysis aimed to address this using data on osteoporotic vertebral compression fractures.⁵³ For acute pain, participants in the calcitonin group and control group, began with no statistical difference in pain scores between the two groups.⁵³ After starting treatment, the results indicated a significant reduction in pain at rest during the first four weeks (mean difference (M.D.) = -3.39 with a confidence interval (CI) = -4.02 to -2.76) and a significant reduction in pain scores with mobility during the fourth week (MD = -5.99, 95% CI = -6.78 to -5.19) in the calcitonin-treated group.⁵³ For chronic pain, there was no significant difference in pain at rest between the calcitonin group and control group at three months (standardized mean difference (SMD) = 0.17, 95% CI = -1.46 to 1.12) and one year (SMD = -0.42, 95% CI = -0.84 to 0.00, $p = 0.05$), but there was a small, statistically significant difference between the groups while mobile at six months (SMD = -0.49, 95% CI = -0.85 to -0.13, $p = 0.008$, $I^2 = 0\%$).⁵³

Elcatonin, eel calcitonin, can also be used to treat acute back pain in patients with osteoporotic vertebral fractures. 228 women with acute lumbar pain from osteoporotic vertebral compression fractures and a mean age of 77.3 years were divided into two groups to receive either oral nonsteroidal anti-inflammatory drug (NSAIDs) or intramuscular injections of elcatonin (20 units) to evaluate the efficacy of eel calcitonin injections.⁴⁹ 20 units of elcatonin were injected once weekly, and the control group was given daily doses of either: loxoprofen sodium (three 60-mg tablets daily), diclofenac sodium (three 25-mg tablets), etodolac

(two 200-mg tablets), lornoxicam (three 4-mg tablets), or zaltoprofen (three 80-mg tablets) with no permission to use any other pain medication.⁴⁹ Pain was assessed with the VAS, and quality of life was assessed with a modified Roland-Morris Disability Questionnaire (RDQ) and the Japanese Questionnaire for Osteoporotic Pain (JQ22) at 4 and 6 weeks.⁴⁹ There was no notable difference in the baseline scores (week 0) of the three outcome measures when comparing the elcatonin and NSAIDs treatment groups.⁴⁹ However, there were statistically significant differences in the three outcome measures at 4 and 6 weeks when comparing the two treatment groups.⁴⁹ The mean difference in outcome measures between the two groups at four weeks demonstrated: -4.8 for JQ22, -1.3 for RDQ, and -11.3 for VAS, and at six weeks demonstrated: -8.3 for JQ22, -2.6 for RDQ, and -11.5 for VAS.⁴⁹ Conclusively, elcatonin treatment demonstrated superior pain relief and improvement in quality of life over the NSAIDs when used shortly following a vertebral fracture, and similar analgesic findings can be found for nasally administered salmon calcitonin as well.⁴⁹

The safety of calcitonin can be assessed through the side effects encountered during randomized controlled trials. One trial found the results of salmon calcitonin to be minimal, excluding nausea and vomiting, which may subside with the continuation of the medication.⁵⁰ However, 80% of subjects in the oral rsCT, ssCT, and placebo group endured at least one adverse event, with abdominal pain and nausea being the most common. Nearly 50% in each group reported gastrointestinal events.⁵⁰ Subjects with severe adverse events were reported by 7.6% in the oral rsCT group, 4.9% in the ssCT group, and 8.7% in the placebo group, but no deaths were reported. In another study, 92% of subjects in the oral calcitonin and placebo groups experienced an adverse event, with the majority being: back pain, joint pain, nasopharyngitis, and hypertension.⁵¹ The oral calcitonin group also experienced: 3-fold increase in nausea, a 6-fold increase in hot flushes, diarrhea, abdominal pain, vomiting, dizziness, hypocalcemia, and muscle spasms compared to the placebo group.⁵¹ However, the placebo group experienced more extremity pain, influenza, bronchitis, musculoskeletal pain, cataracts, viral infection, insomnia, peripheral edema, chest pain, and upper respiratory tract infections when compared to the oral calcitonin group.⁵¹ Overall, the oral calcitonin group reported 78.8% of the adverse events to be mild, 64.4% to be moderate, and 14.8% to be severe.⁵¹ The number of severe events encountered was comparable between the oral calcitonin (2.83%) and placebo (3.00%) groups and included occurrences such as cardiac events, injuries, neoplasms (basal cell carcinoma and breast cancer), and infections.⁵¹ Oral calcitonin was found to have minimal side effects and is as well tolerated as the nasally administered or placebo groups. Elcatonin injections are a safe and effective treatment with almost no reports of cancer in post-marketing surveillance.⁴⁹⁻⁵¹ Recording of cancer was a distinct concern in this study because cancer has been noted as a side effect of calcitonin therapy, but there were differences in cancer occurrences between the oral calcitonin group and placebo group in this controlled trial.^{51,54,55}

Table 1. Clinical Efficacy and Safety

Study type	Author (year)	Groups studied and intervention	Results and Findings	Conclusions
Randomized, double-blind, double-dummy, active- and placebo-controlled, multiple-dose, phase 3 study	50	Postmenopausal women diagnosed with osteoporosis were divided into 3 groups to receive: oral recombinant salmon calcitonin with placebo nasal spray, synthetic salmon calcitonin nasal spray with placebo tablets, and placebo tablet and placebo spray.	Women in the oral rsCT group had a greater increase in lumbar spine BMD from baseline than the other two groups and a greater BMD in trochanteric and total proximal femur when compared to just the ssCT group. There were significant reductions in 2/3 bone resorption markers in the rsCT group when compared to the ssCT group, and a reduction in 3/3 markers when rsCT compared to the placebo group. 80% of the participants experienced at least 1 adverse event, and less than 10% in each group experienced a serious adverse event.	Oral rsCT showed improved BMD and less bone turnover when compared to nasal ssCT or placebo and may be used as alternative therapy in postmenopausal osteoporotic women. Oral rsCT was found to have minimal side effects and is as well tolerated as the ssCT or placebo groups.
Randomized, double-blind, placebo-controlled phase III study	51	3310 postmenopausal osteoporotic women were divided into two groups and given either: oral calcitonin or placebo.	Oral calcitonin does not affect preventing new vertebral fractures, hip, or non-vertebral fractures. There was a slight increase in BMD of the lumbar spine, femoral neck, and hip in both groups. Less bone turnover was noted at 12 and 24 months, but not at 36 months in the oral calcitonin group, with no change in the quality of life between the groups. 92% of all subjects reported an adverse event, most of which were mild or moderate. The oral calcitonin group experienced more nausea, vomiting, abdominal pain, and hot flushes when compared to the placebo.	This fracture efficacy trial failed to result in any clinical benefit of subjects taking oral calcitonin, attributed to low drug exposure levels.
Prospective, double-blind, randomized, placebo-controlled, clinical trial	52	40 patients who recently suffered a non-traumatic osteoporotic vertebral fracture received either a calcitonin or placebo suppository once daily with or without also taking paracetamol (500mg) tablets.	The calcitonin suppository group experienced less spinal pain, early mobilization, sitting, walking, and standing when compared to the placebo suppository group. There was also less bone turnover in the calcitonin suppository group.	Salmon calcitonin suppositories caused a significant decrease in spinal pain in patients with nontraumatic osteoporotic vertebral fractures that occurred within 5 days of treatment. This induced return of locomotor functions.
Nationwide, prospective, multicenter, open-label, randomized controlled trial	49	Osteoporotic women with acute lumbar pain after a new vertebral compression fracture were divided into two treatment groups: 114 received 20 units of elcatonin injected once weekly, and 114 women received NSAIDs daily for 6 weeks.	There were statistically significant differences between the two treatment groups measured through the VAS of pain intensity and quality of life measured by the JQ22 and RDQ. The mean differences between the elcatonin group and the NSAIDs group in each measure at 4 and 6 weeks were -4.8 and -8.3 for the JQ22, -1.3 and -2.6 for the RDQ -11.3 and -11.5 for the VAS, in favor of elcatonin.	Once weekly injections of elcatonin were more efficacious than daily NSAIDs when managing pain and improving mobility after an osteoporotic fracture
Systematic review and meta-analysis	53	13 different studies/trials were reviewed and analyzed to study calcitonin as a treatment for acute and chronic pain at rest and while mobile after suffering an osteoporotic vertebral compression fracture. The studies included: 4	Calcitonin significantly reduced acute pain at rest and mobile. There was no difference in chronic pain in patients treated with calcitonin or control groups.	Calcitonin has proven value in treating acute back pain associated with recent osteoporotic vertebral compression fractures. Still, there

Study type	Author (year)	Groups studied and intervention	Results and Findings	Conclusions
		trials studied acute pain at rest, four trials studied acute pain with mobility, 2/5 studies reviewed chronic pain at rest, 4/5 studies examined chronic pain with mobility.		is no evidence to support the use of calcitonin for chronic pain associated with older fractures.

CONCLUSION

Osteoporosis and its associated complications, such as vertebral compression fractures, impact large portions of the population and represent a significant clinical burden to the healthcare system. Continued investigation into the management of VCF aims to provide pain and symptom relief. Traditional conservative therapies aim to manage pain through oral analgesics and physical therapy. More invasive procedures, such as kyphoplasty or vertebroplasty, may be pursued for patients requiring further management of pain and fracture complications.

Calcitonin is a safe and effective option for patients, especially for those who cannot tolerate more traditional methods of pain management or who have failed initial treatment. Its added benefits of increasing bone mineral density make it particularly apt to treat VCFs and address pain management, and it poses few severe side effects. Fur-

ther research is needed to fully understand calcitonin's potential role as a preventative therapy in reducing the incidence of future fracture, which would offer another critical advantage in treating osteoporosis and associated VCFs.

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