Efficacy of calcitonin for treating acute pain associated with osteoporotic vertebral compression fracture: an updated systematic review

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CLINICIAN'S CAPSULE

What is known about the topic?
Emergency department physicians commonly manage acutely painful osteoporotic vertebral compression fractures resulting from minor trauma and seek nonopioid alternatives.

What did this study ask?
What evidence exists on the efficacy of calcitonin for managing acute pain associated with compression fractures?

What did this study find?
Calcitonin significantly reduced acute compression fracture pain (number needed to treat = 2) and improved function without significantly increasing the overall risk of side-effects.

Why does this study matter to clinicians?
Calcitonin appears to be an effective and safe alternative for the short-term management of acutely painful compression fractures.

ABSTRACT

Objective: Acutely painful osteoporotic vertebral compression fractures are associated with hospitalization and mortality in older adults. Calcitonin may be an alternative to opioid or nonopioid analgesia for treating acute compression fracture pain in emergency and primary care settings. This review summarizes pain, function, and adverse events associated with calcitonin.

Methods: We searched MEDLINE, EMBASE, The Cochrane Library, clinical trials registries, and reference lists of included studies. Eligible studies evaluated the effect of synthetic calcitonins (salmon, eel, and human) on pain scores in adults ≥60 years old with a recent atraumatic compression fracture. Two reviewers screened studies, extracted data, and allocated bias in duplicate. A random effects meta-analysis evaluated standard mean difference (SMD) and heterogeneity (I^2).

Results: Of 1,198 articles screened, 11 were included (9 in the meta-analysis). Treatment lasted from 14 days to 6 months. Pain was lower in the salmon calcitonin group (100–200 IU IM or NAS, daily) than the control group with high certainty of evidence at week 1 (SMD, -1.54; 95% confidence interval [CI], -2.02 – -1.06; $I^2 = 52\%$), representing a number needed to treat of two. The analgesic efficacy of salmon calcitonin at 4 weeks was unclear due to substantial heterogeneity. There was low certainty evidence that calcitonin did not increase the overall risk of adverse events, including nausea and vomiting (risk ratio, 2.10; 95% CI, 0.87–5.08; $I^2 = 47\%$).

Conclusions: Calcitonin is beneficial and appears safe for treating acute pain associated with compression fractures. Further studies may improve the certainty of evidence.

RÉSUMÉ

Introduction : Les fractures ostéoporotiques par tassement vertébral causent de vives douleurs et sont associées à l'hospitalisation et à la mortalité chez les personnes âgées. La calcitonine pourrait être une solution de rechange aux analgésiques de type opioïde ou non dans le traitement de la douleur aiguë due à des fractures par tassement, au service des urgences et dans les milieux de soins primaires. Suivra un résumé de l'effet de la calcitonine sur la douleur et sur la capacité fonctionnelle ainsi que des événements indésirables associés au médicament.

Méthode : Une recherche a été entreprise dans les bases de données MEDLINE, EMBASE, The Cochrane Library et les registres d'essais cliniques, ainsi que dans les listes de références bibliographiques des études retenues. Étaient sélectionnés les travaux qui portaient sur l'effet de la calcitonine synthétique (de saumon, d'anguille ou humaine) sur la cotation de la douleur chez des personnes de ≥ 60 ans, ayant subi une fracture récente par tassement, sans trauma. Deux examinateurs ont procédé au choix des études, à l'extraction des données, puis à l'appréciation du risque de biais dans les études de même nature. L'évaluation de la différence des

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moyennes standardisées (DMS) et de l'hétérogénéité (I2) a été effectuée par méta-analyse à effets aléatoires.
Résultats : Sur 1198 articles initialement retenus, 11 ont été sélectionnés (dont 9 dans la méta-analyse). La durée du traitement variait de 14 jours à 6 mois. Le soulagement de la douleur était plus marqué dans le groupe de la calcitonine de saumon (100-200 UI, i.m. ou i.n. [intranasale], tous les jours) que dans le groupe témoin, soulagement qui a atteint un degré de certitude élevé à la 1re semaine (DMS : -1,54; intervalle de confiance à 95 % [IC] : -2,02 à -1,06; I2 : 52 %) et qui représentait le nombre de sujets à traiter, soit 2. Toutefois, l'efficacité analgésique de la calcitonine de saumon s'est estompée au bout de 4 semaines en raison d'une forte hétérogénéité. Enfin, d'après des données de faible certitude, la calcitonine n'augmentait pas le risque global d'événements indésirables tels que les nausées et les vomissements (risque relatif : 2,10; IC à 95 % : 0,87-5,08; I2 : 47 %).
Conclusion : La calcitonine produit un effet bénéfique et semble sûre dans le traitement de la douleur aiguë due à des fractures par tassement. La réalisation d'autres études pourrait toutefois améliorer le degré de certitude des données.

INTRODUCTION

Compression fractures of the vertebrae represent a common type of osteoporotic fracture and are a common cause of emergency department (ED) visits and functional decline in the elderly.[1,2] The lifetime risk of developing a painful compression fracture is 18% among females and 11% among males 60 years of age; however, many fractures are asymptomatic.[3] Acutely painful compression fractures tend to be precipitated by minor falls, bending, or twisting motions, and one case purportedly occurred while driving over a speed bump.[4–6] Compression fractures result in more acute care admissions in Canada than any other osteoporosis-related fracture type, except for hip and femur fractures.[2] Moreover, compression fractures result in substantial health care usage and costs. In Canada, 36% of patients with ICD-10-CA codes for vertebral fracture attributable to osteoporosis were hospitalized within 1-year of their fracture, with a mean length of stay of 15 (standard error = 0.5) days.[2] Acute pain associated with compression fractures ranges from mild to severe, and is treated with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids when additional pain relief is required. However, NSAIDs carry increased risks of gastrointestinal (GI) toxicity and renal insufficiency in older adults,[7] and along with opioids are associated with adverse events related to drug interactions.[8] In addition, their efficacy in treating pain associated with compression fractures has not been demonstrated.

Canadian clinical practice guidelines for osteoporosis suggest treating compression fracture-related pain with calcitonin; however, there is limited evidence to support this off-label use of the drug.[9] Calcitonin is produced by C-cells of the thyroid and may reduce the transmission of pain signals by the central and peripheral nervous systems through increasing the secretion of beta-endorphins by neurons and decreasing cyclooxygenase, respectively.[10,11] There are multiple synthetic formulations of calcitonin; however, only salmon calcitonin is available in Canada. Data from new randomized controlled trials and trials missed previously may influence the findings reported in a prior systematic review on this topic by Knopp-Sihota et al. (2012) and their credibility.[12] In addition, the effects of calcitonin on secondary outcomes, including function has not yet been evaluated.[12,13] Therefore, the objective of this systematic review is to systematically evaluate the efficacy of calcitonin in treating acute pain and evaluate its impacts on secondary outcomes, including length of hospital stay, ability to function, and quality of life.

METHODS

Study design and registration

We conducted this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1) (Figure 1). The study protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO-CRD42018084850).[14]

Search strategy

MEDLINE, EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews), Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry

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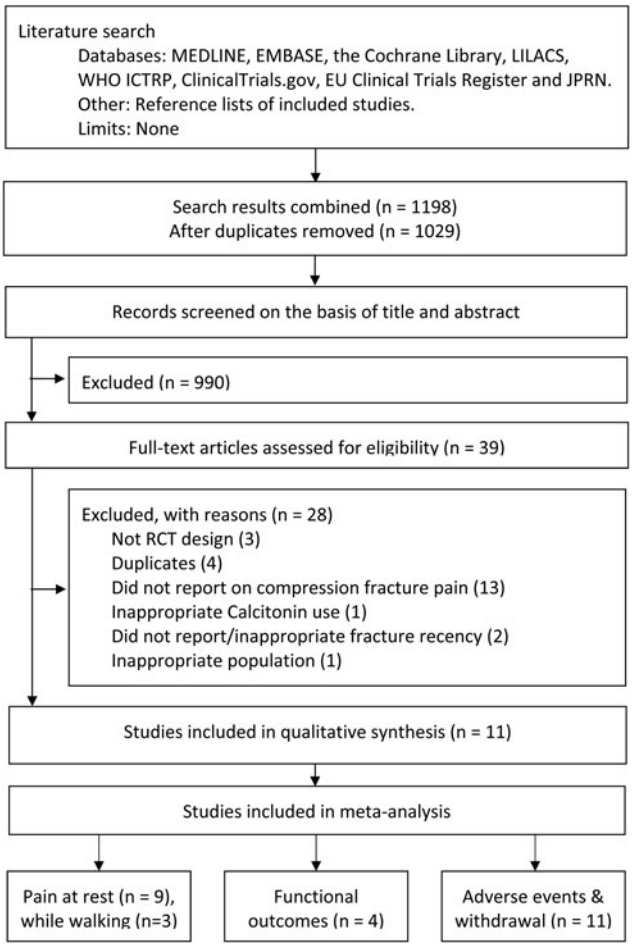

Figure 1. PRISMA flow diagram

Platform, ClinicalTrials.gov, EU Clinical Trials Register, Latin American and Caribbean Health Sciences Literature Database, and Japan Primary Registries Network were searched without limits with assistance from a librarian (L.T.). Conference papers and reference lists of included studies were also searched. The search strategy was developed using Medical Subject Headings (MeSH) related to compression fracture, calcitonin, and pain (Supplemental Files).

Inclusion criteria

Randomized-controlled trials that enrolled older adults (mean >60 years of age) who suffered acute pain associated with a recent compression fracture (<16 weeks) were included. This definition was chosen because, while most clinical osteoporotic vertebral compression fractures result in the rapid onset of severe pain, some may present with multiple bouts of acute pain of lesser severity over a period of weeks to months.[15] Studies that evaluated calcitonin (any route of administration, analogue, or dose) were considered for inclusion.

Data extraction and risk of bias assessment

Two reviewers (E.B., B.R.) extracted data and allocated bias using the Cochrane Collaboration's tool for risk of bias assessment independently and in duplicate using a standardized form. Trial investigators were contacted to obtain missing data. In cases where results were shown as graphs and original results were unavailable, data were extracted from figures using a Web-based tool.[16] Disagreement between reviewers was resolved by a third reviewer (E.L.).

Statistical analysis

Included studies were grouped by the timing of outcome measures: 1 and 4 weeks. For pain and function scores, continuous outcomes reported as means with standard deviations were pooled for meta-analysis using a random-effects model to account for unexplained heterogeneity.[17] Standard mean difference (SMD) and 95% confidence intervals (CIs) were calculated. To aid in the interpretation of the SMD, the probability of benefit (POB), which represents the probability that a person from the treatment group has a lower pain score than a person in the control group and number needed to treat (NNT) were determined as described by Kraemer and Kupfer.[18,19] For the analysis of adverse events and study withdrawal, dichotomous outcomes were pooled and risk ratios (RRs) with 95% CIs were calculated using the Mantel-Haenszel approach.[17] For adverse events with five or more occurrences, p-values were computed with Fisher's exact test (two-tailed).

Assessment of heterogeneity

Between-study heterogeneity was assessed qualitatively and using I^2 and the χ^2 test (>75% or <0.1, indicative of substantial heterogeneity, respectively).[17] Subgroup analyses were performed to explore sources of heterogeneity. We decided a priori to conduct subgroup analyses for type of calcitonin.

p-values of < 0.05 were considered significant. All statistical analyses were performed in RevMan (version 5.3.5), except POB, NNT, and Fisher's exact test,

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which were calculated in RStudio (version 1.1.453) and GraphPad (version 8), respectively.

Grading of evidence

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were considered.[20]

RESULTS

Our search yielded 1,198 records, of which 39 full-text articles were screened. Common reasons for the exclusion of records were related to study design and outcome, for example evaluating the efficacy of calcitonin for preventing of fractures instead of treating fracture pain. Eleven studies were included in the systematic review, with 713 participants.[21–31] Two studies could not be pooled for meta-analysis of the primary outcome, pain at rest, because data were reported as median values and without a measure of variance[28,30]; thus, nine studies were considered for meta-analysis of pain at rest with 641 participants, of whom 94.6% were female.[21–27,29,31]

Characterization of included studies

Study design and participants

Participants in included studies were generally between 60 and 70 years of age and presented with acute back pain attributed to compression fracture by clinical examination alone[31] or in combination with X-ray and MRI imaging.[21,23–31] Fractures resulting from high-impact trauma, malignancies, and bone metabolism disorders were excluded; however, no included studies specified the mechanism of injury.[21–31]

Interventions and outcomes

Intervention groups received calcitonin as an intramuscular (IM)[21–24,26,31] or subcutaneous (SC) injection,[30,31] intravenous (IV) infusion,[25] intranasal spray (NAS)[27,29] or suppository.[28] Doses were 20 IU per week for elcatonin IM (synthetic eel calcitonin),[21–23] 50–100 IU per day for synthetic salmon calcitonin IM, SC, or NAS,[24,26–31] and 1.5 mg over a 4-hour IV infusion for synthetic human calcitonin.[25] Studies used a placebo[26–31] or active treatment of bisphosphonates/anti-osteoporosis drugs[22,24,25] or NSAIDs[21,23] in comparator groups. Nine studies permitted participants randomized to either group to take rescue analgesics (NSAIDs, acetaminophen, or unspecified).[21–23,25–30] Follow-up time ranged from 14 days to 6 months. All included studies scored pain using self-reported visual analogue scales.[21–31] Five studies scored participant's self-reported function, including their ability to perform activities of daily living independently.[21,23–25,30] Length of hospital stay, health-related quality of life, and compliance were not reported by any included studies (Supplemental Table S1).[21–31]

Risk of bias

Risk of bias is summarized in Supplemental Figure S1. The majority of studies were double-blind[25–31]; however, results from open-label[21–23] and single-blind design[24] studies may be affected by performance and/or detection bias. Randomization and allocation concealment were specified in three[23,24,29] and two,[21,22] trials, respectively. Selective reporting and incomplete reporting of outcome data were uncommon.[27,28]

Analgesic efficacy of calcitonin

All included studies reported that calcitonin significantly reduced acute pain associated with recent compression fractures.[21–31] Data were grouped based on type of calcitonin and dose due to the presence of heterogeneity (I^2 = 90% at 1 week and 93% at 4 weeks; Supplemental Figure S2). Salmon calcitonin improved pain scores at 1 week (SMD, -1.54; 95% CI, -2.02 – -1.06) (Figure 2) with a high certainty of evidence as assessed with GRADE criteria.[24,26,27,29] The POB for salmon calcitonin at 1 week was 86.2% (95% CI, 77.3–92.3%), representing a NNT of 2 (95% CI, 2–2). At 4 weeks, a high level of heterogeneity was present (I^2 = 95%); thus, the data were not pooled (Figure 3).[24,27,29,31] Weekly elcatonin modestly improved pain scores at 4 weeks (SMD, -0.41; 95% CI, -0.62 – -0.20; Figure 3),[21–23] but not 1 week (SMD, -0.09; 95% CI, -0.42–0.25; Figure 2).[21,22] The certainty of evidence was downgraded to moderate due to concerns about detection and performance bias (Table 1).

Effects of calcitonin on function

At 1 week, function was improved after daily treatment with salmon calcitonin in one study; however, weekly treatment with elcatonin did not (data not pooled due

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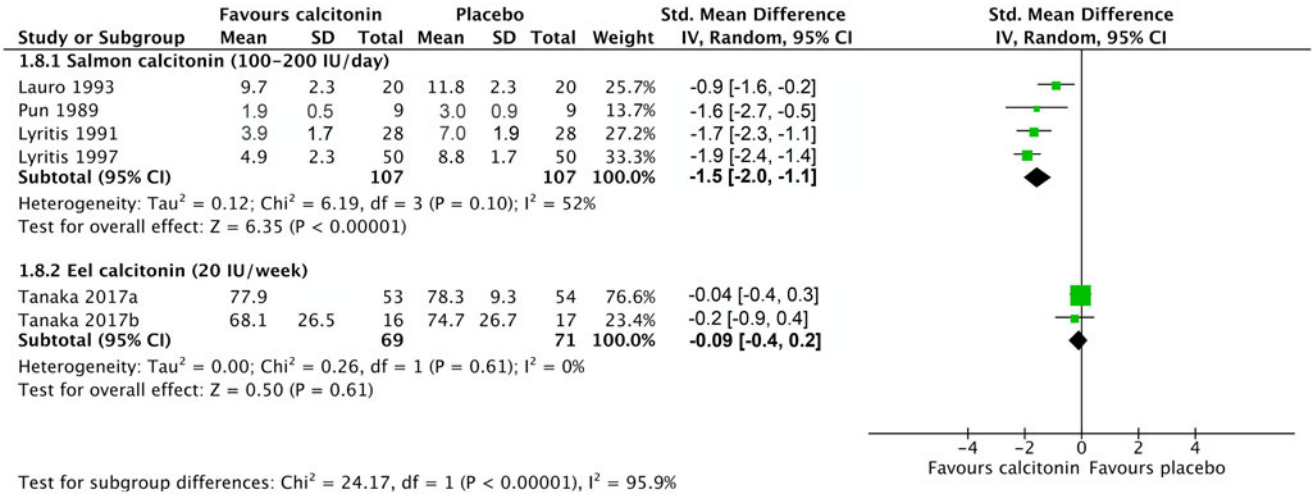

Figure 2. The effects of elcatonin, salmon, and synthetic human calcitonin on pain associated with compression fracture after 1 week of treatment

to heterogeneity, $I^2 = 78\%$).[21,24] At 4 weeks, all types of calcitonin improved function (SMD, -0.48; 95% CI, -0.79 – -0.17)[21,23–25] with a POB of 63.3% (95% CI, 71.2–54.8%) and NNT, 4 (95% CI, 3–11). The level of certainty for both time points was low.

Adverse events and study withdrawal

Seven hundred thirteen patients across 11 studies had a nonsignificantly higher risk of developing adverse events (RR, 2.10; 95% CI, 0.87–5.08; $I^2 = 47\%$) with low certainty (Figure 4). The certainty of evidence was downgraded due to imprecision and concerns about bias introduced by open-label and single-blind studies. Nausea, vomiting, and enteric side effects were reported by 22 participants in calcitonin treatment groups, but were not significantly increased compared with the control group ($p = 0.511$).[23,24,26,28,30] Eleven participants reported mild or nonspecific side effects, including hot flushes, redness, and injection site pain (Table 2).[23,25–27,30] Twelve

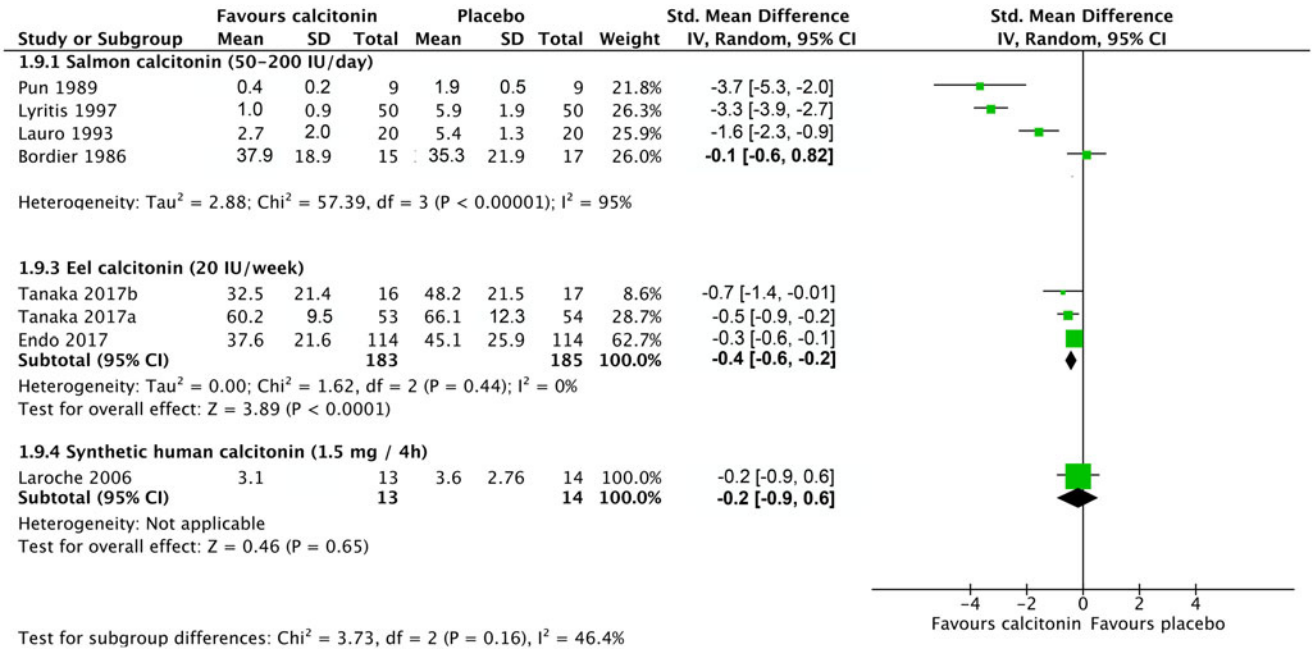

Figure 3. The effects of elcatonin, salmon, and synthetic human calcitonin on pain associated with compression fracture after 4 weeks of treatment

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Table 1. Summary of findings table for key outcomes including assessment with GRADE

Key outcomes			No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
						Risk with placebo	Risk difference with calcitonin
Pain at rest	1 week	Salmon calcitonin (100–200 IU/day)	214 (4 RCTs)	⊕⊕⊕⊕ HIGH *,†	–	–	SMD 1.54 lower (2.02 lower to 1.06 lower)
		Eel calcitonin (20 IU/week)	140 (2 RCTs)	⊕⊕⊕◯ MODERATE ‡	–	–	SMD 0.09 lower (0.42 lower to 0.25 higher)
	4 weeks	Salmon calcitonin (50–200 IU/day)	190 (4 RCTs)	⊕⊕⊕◯ MODERATE *,†,§,¶	–	Not pooled	Not pooled
		Eel calcitonin (20 IU/week)	354 (3 RCTs)	⊕⊕⊕◯ MODERATE‡	–	–	SMD 0.41 lower (0.62 lower to 0.2 lower)
		Synthetic human calcitonin (1.5 mg / 4h)	27 (1 RCT)	⊕◯◯◯ VERY LOW *,§	–	–	SMD 0.18 lower (0.93 lower to 0.58 higher)
Adverse events			699 (11 RCTs)	⊕⊕◯◯ LOW §,¶	RR 2.10 (0.87 to 5.08)	54 per 1,000	60 more per 1,000 (7 fewer to 222 more)

Note: The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
*Trials have small n (n < 100).
†No prospective protocols were available.
‡Studies were unblinded or single-blinded.
§Substantial unexplained heterogeneity.
¶Wide CIs.
#Assessed at a range of time points (1–6 months).

participants withdrew from four studies due to a desire for stronger analgesia (n = 6 in placebo groups), erythema (n = 3), enteric disturbances (n = 3), or unspecified reasons (n = 2).[23,25,28,30] Five participants were lost to follow-up.[23]

Interpretation

This systematic review synthesizes the findings of 11 randomized-controls trials investigating the efficacy of calcitonin for treating acute pain associated with compression fractures. High quality evidence was found supporting the efficacy of salmon calcitonin for reducing compression fracture pain after 1 week of treatment, which is consistent with previous studies.[13,14] The narrative synthesis suggests salmon calcitonin may reduce pain at later time points; however, data could not be pooled due to substantial heterogeneity between studies. Low certainty evidence showed that low-dose elcatonin improved pain after 4 weeks, but not 1 week. The effect of calcitonin on function has not been reported in previous reviews, but is relevant due to its association with ED visits in the elderly.[32] Salmon calcitonin and elcatonin were found to improve function over longer time periods with low certainty evidence. There was low certainty evidence that calcitonin does not increase the risk of adverse events. Adverse events reported in included studies were similar to those described for other indications of calcitonin.

No studies have directly compared the efficacy of salmon calcitonin against elcatonin, which is used in Japan, but is not approved by Health Canada.[23,33] It is unclear if the lack of efficacy of elcatonin is related to the low dose used (20 IU per week) relative to studies evaluating salmon or synthetic human calcitonin. It is possible that the effect between salmon calcitonin and elcatonin may be confounded by other factors, such as route of administration. A double-blind equivalence study comparing SC and NAS calcitonin formations for the relief of acute pain resulting from compression fractures found there was no difference in effect based on the route of administration.[34] Thus, these potential confounders are unlikely to account for this finding.

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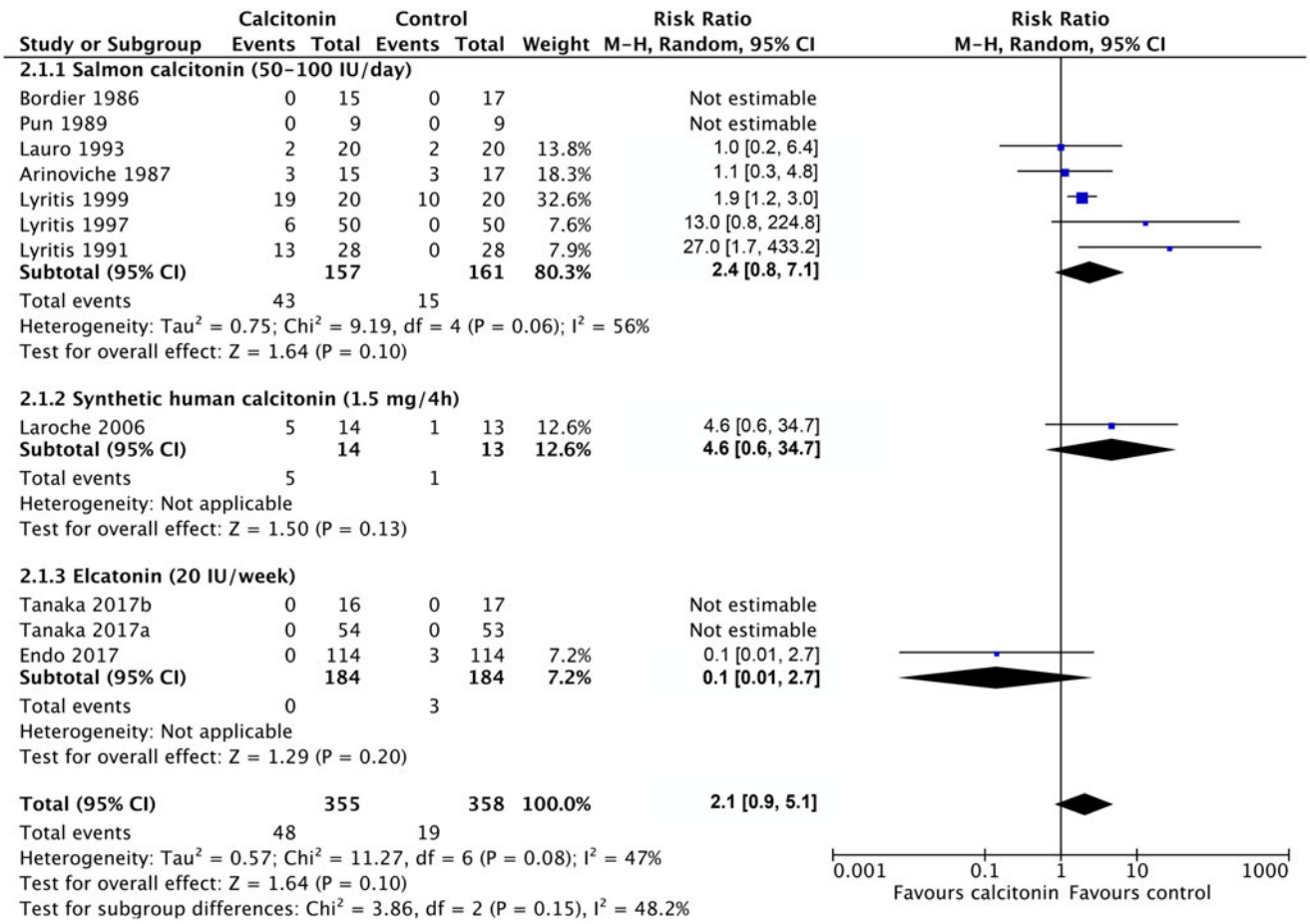

Figure 4. Relative risk of adverse events associated with calcitonin use to treat pain associated with compression fracture

The results of our study indicate that salmon calcitonin may be an appropriate adjunct treatment for reducing pain in elderly patients with compression fractures and no new neurologic injury who have received the maximum dose of acetaminophen. NSAIDs and other narcotics are commonly contraindicated in older adults with comorbid conditions[35]; therefore, calcitonin is a promising therapy for pain reduction. In addition, the adverse events reported with calcitonin use appeared mild and may be superior to those associated with NSAIDs and opioids in elderly persons.[35] Treatment with 50–200 IU IM or NAS salmon calcitonin, daily for 1 week was effective at reducing pain.[24,26,27,29] In Canada, 1 U of calcitonin (200 IU for injection) costs of $30.48.[36]

Table 2. Adverse events

Adverse event	No. in calcitonin group / 355 (%)	No. in placebo group / 358 (%)	Fischer's exact *p*-value
Nausea, vomiting, and GI disturbance	22 (6.2%)	11 (3.1%)	0.05
Dizziness	8 (2.3%)	1 (0.3%)	0.02
Loss of appetite	7 (2.0%)	–	0.01
Injection site pain	7 (2.0%)	–	0.01
Headache	6 (1.7%)	–	0.02
Hot flushes	5 (1.4%)	0	0.03
Muscle pain	0	1 (0.3%)	–
Rash	0	2 (0.6%)	–

The long-term use of calcitonin nasal sprays appears to be associated with a slight increase in cancer risk,[37,38] although none of the included studies reported cancer as an adverse event.[21–31] Health Canada withdrew nasal salmon calcitonin, because it no longer has a favorable risk–benefit profile for treating osteoporosis and recommended that the use of injectable calcitonin be limited to less than 3 months.[37] Further research is required to clarify the safety of short-term use of calcitonin. However, the results of this study suggest that

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the short-term use of calcitonin may still be beneficial for treating acute pain associated with compression fractures in older adults. Calcitonin may be initiated by the emergency physician and continued by the patient's family doctor if appropriate. The decision to use calcitonin should reflect the patient's values and preferences, because pain relief may be prioritized over a small increase in cancer risk by some individuals.

LIMITATIONS

We followed rigorous protocol (PRISMA), prospectively registered our study and conducted a comprehensive search of electronic databases, clinical trials registries and grey literature. A random effects model, which tends to produce more conservative effect-sizes, was used and the inclusion of extremely small studies did not appear to artificially increase the effect size. The decision to conduct a subgroup analysis based on the type of calcitonin used was made a priori. Consequently, the pooled effect size was derived from a small number of trials and may have limited generalizability. The small sizes of included trials might have contributed to imprecise effect sizes. We were unable to assess outcomes based on pain severity through subgroup analyses, because all studies reported moderate-to-severe pain at baseline. Future studies should evaluate outcomes based on pain severity, because these results may underestimate the beneficial effects of calcitonin for mild-to-moderate pain. Osteoporotic patients were identified based on clinical exam and X-ray or MRI interpretation in all included studies except one,[31] which are subjective and might have contributed to heterogeneity. Finally, although our results were obtained from a comprehensive review of the published literature, there is the potential for unpublished negative trials to introduce bias. Future randomized-trials must strengthen the base of evidence for calcitonin as an analgesic.

CONCLUSIONS

Short-term use of salmon calcitonin, but not low-dose elcatonin, appeared to reduce acute pain associated with compression fracture in older adults without significantly increasing the risk of adverse events. Both types of calcitonin may improve function after compression fractures. Calcitonin may be considered as an alternative to opioid and nonopioid analgesic in older adults with compression fractures in emergency and primary care settings, but should be used on a short-term basis only due limitations in the evidence.

Supplemental material: The supplemental material for this article can be found at https://doi.org/10.1017/cem.2019.490

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