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REVIEW

Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis

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Abstract Vertebral collapse is a common fracture associated with osteoporosis. Subsequent pain may be severe and often requires medications and bed rest. Several studies have suggested the use of calcitonin for the treatment of fracture pain. We sought to determine the analgesic efficacy of calcitonin for acute and chronic pain of osteoporotic vertebral compression fractures (OVCF). We searched for randomized, placebo, and controlled trials that evaluated the analgesic efficacy of calcitonin for pain attributable to OVCFs. We performed meta-analyses to calculate standardized mean differences (SMDs) using a fixed or random effects model. The combined results from 13 trials (n=589) determined that calcitonin significantly reduced the severity of acute pain in recent OVCFs. Pain at rest was reduced by week 1 [mean difference (MD)=−3.39, 95% confidence interval (CI)=−4.02 to −2.76), with continued improvement through 4 weeks. At week 4, the difference in pain scores with mobility was even greater (SMD=−5.99, 95% CI=−6.78 to −5.19). For patients with chronic pain, there was no statistical difference between groups while at rest; there was a small, statistically significant difference between groups while mobile at 6 months (SMD=0.49, 95% CI=−0.85 to −0.13, p=0.008). Side effects were mild, with enteric disturbances and flushing reported most frequently. Although calcitonin has proven efficacy in the management of acute back pain associated with a recent OVCF, there is no convincing evidence to support the use of calcitonin for chronic pain associated with older fractures of the same origin.

Keywords Back pain · Calcitonin · Osteoporosis · Vertebral fractures

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Introduction

Background

Osteoporosis is a serious public health problem for older adults, with an estimated 1.4 million Canadians and 10 million Americans affected [1, 2]. The epidemiological and clinical importance of osteoporosis lies in the fractures that are associated with the disease, with over 70% of all fractures in older adults being attributed to osteoporosis [3]. Although osteoporotic fractures may occur at multiple sites, vertebral collapse is one of the most common; in developed countries like Canada, the lifetime risk of an osteoporotic vertebral compression fracture (OVCF) is one in four among women and one in eight among men, and increases in prevalence with age in both sexes [2]. Not only is the

condition common, it is also costly; in 2005, in the USA alone, patients sustained more than 2 million fractures, costing the health care system nearly US $17 billion [4].

Description of the condition

An OVCF can be diagnosed radiographically or as a symptomatic clinical event whereby patients present with back pain typically of sudden onset associated with a relatively atraumatic event such as bending or coughing [5]. When an acute OVCF occurs, the pain may be so devastating and disabling that hospital admission is required; length of stay for such fractures may be as long as 10 to 14 days [6–8]. On the other hand, OVCFs may be associated with mild back pain and stiffness, and the diagnosis of a fracture often goes unnoticed [9]. Although many patients with OVCF experience a predictable improvement in pain over 6–8 weeks [7], some patients experience persistent pain and disability. Multiple OVCFs can lead to a gradual but noticeable loss of vertebral height, leading to progressive dorsal kyphosis. Chronic back pain may result from the associated deformity, joint incongruity, and tension on muscles and tendons; consequently, a significant impairment in spinal range of motion and physical function, including mobility, and lower overall quality of life may be reported [10, 11].

Description of the intervention

The pain of an OVCF is often treated with standard analgesics, although these commonly used analgesics (e.g., acetaminophen with codeine) and non-steroidal anti-inflammatory drugs are not always helpful or appropriate in the older adult population. Sedative–hypnotic medications and narcotics are frequently prescribed for patients with fractures; however, these agents are often associated with important and dangerous side effects [12].

A number of studies have suggested the use of calcitonin as an initial and adjunctive treatment for acute, severe, and unrelenting back pain secondary to fracture as calcitonin exhibits known analgesic properties [13–15]. Some studies have suggested that calcitonin may also be useful in the treatment of chronic back pain related to a more remote OVCF [16, 17]. Calcitonin is a 32-amino acid polypeptide produced and secreted by the thyroid gland of mammals and is available as a nasal spray [intranasal (IN)], an injection [intramuscular (IM) or subcutaneous (SQ)], and as a rectal suppository [18]. Although a number of mechanisms have been suggested, there are two most likely hypotheses explaining the analgesic mechanism of calcitonin: a direct central nervous system action involving calcitonin-binding receptors and an increase in plasma β-endorphin levels [19, 20].

Relevance of systematic review and meta-analysis

The original Cochrane style systematic review on this topic [21] was published in 2005 and focused solely on the acute pain of recent OVCFs. This review not only provides an update to the previous results but also adds an additional dimension related to the use of calcitonin for chronic pain of more remote OVCFs. Given the morbidity associated with these types of fractures, and the frequent necessity of providing analgesia for patients with acute and chronic fracture pain, it is important to determine the effectiveness of calcitonin for both indications. Therefore, we conducted a formal Cochrane style systematic review and meta-analysis of controlled trials to examine the analgesic efficacy of participants receiving calcitonin (any route) compared with a control group receiving either a placebo, no intervention, or "usual care" in older adults with acute (onset <10 days) or chronic pain (>3 months) attributed to a recent or remote OVCF.

Objectives

The objectives of this systematic review were:

1. To assess the analgesic effects of calcitonin (any route), as judged by a quantitative pain scale, in older adults with acute or chronic pain of a recent or remote OVCF,
2. To assess concomitant consumption of other analgesic drugs, side effects, and withdrawals from studies (based on route of calcitonin administration), and
3. To update the previous systematic review with the latest evidence.

Methods

We followed the procedures for conducting systematic reviews and meta-analysis as outlined by the Cochrane Collaboration [22] and the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [23].

Criteria for considering studies for this review

Types of studies

We planned to include a broad range of controlled comparison studies: randomized controlled trials (RCTs), controlled trials, and controlled before and after studies. As there were few such experimental studies, we planned to include observational studies if they included a control group, to compare outcomes. The studies needed to

compare the analgesic effect of calcitonin to either placebo, to no intervention, or to "usual care," in any setting (including acute care hospital, rehabilitation facility, nursing homes, and the community), published in any language, and for which adequate information was provided or could be obtained from the primary researchers. Retrospective studies and studies in which there was no comparison group were excluded from the review.

Types of participants

To be eligible for inclusion, studies needed to involve older adults (aged 60 years and older) of either sex who suffered from acute (onset <10 days) or chronic back pain (>3 months) associated with a clinician diagnosis of an OVCF (by radiograph or clinical presentation) who received calcitonin (any route and any dose) or placebo or "usual care." Patients may have resided in any health care facility (acute or rehabilitation care), a community care setting (nursing home or assisted living), or in their own homes.

Types of interventions

Studies were included if they evaluated the effectiveness of calcitonin given by any route to achieve analgesia. Comparative treatments included placebo, usual treatment, or other known analgesics. Trials that compared different doses or routes of calcitonin, with no inactive comparator group, were excluded.

Types of outcome measures

All clinical outcomes were considered; however, the primary outcome of interest was the analgesic efficacy of calcitonin as judged by a quantitative pain scale [e.g., visual analogue scale (VAS)]. Pain scores ideally were assessed with patients at rest, sitting, standing, and walking in order to describe not only pain relief but also the length of time to mobilization. The concomitant consumption of other analgesic drugs, side effects, and withdrawals from studies (based on route of calcitonin administration) were also examined. A priori, we planned subgroup analyses based on: the sex and age of participants, route of calcitonin administration, and acute vs. chronic pain.

Search methods for identification of studies

Studies were identified by several methods. First, we searched for randomized trials in the Cochrane Musculoskeletal Group specialized trial register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966–present), EMBASE (1988–present), and the LILACS (Latin American and Caribbean Computer Library Center) databases. Gray literature was searched using "Dissertation Abstracts and Index to Theses." All databases were last accessed in October 2010. We used the following text words and Medical Subject Headings: *calcitonin*; *osteoporosis*; *vertebral compression fracture*; *analgesia*; *pain control*; *aging*; *elderly*; *placebo*; and *clinical trial*. In addition, the reference lists of all relevant articles were examined for further pertinent studies and conference proceedings were sought from various web sites and organizations. Forward citation searches of included studies and relevant literature reviews were also done. Primary authors, experts in the field, and the manufacturer of calcitonin (Novartis) were contacted to identify additional published, unpublished or "in-progress" studies. The search was not limited by language or publication status. See Appendix 1 for details of the MEDLINE search; this search strategy was adapted for all electronic search engines.

Data collection and analysis

Selection of studies

One of the study investigators (JKS) performed the initial search of all databases to identify potentially relevant citations. Where it was not possible to accept or reject the study, the full text of the citation was obtained for further evaluation. Following the screening of titles and abstracts, the full texts of potential articles were retrieved (and translated into English where required) and assessed independently by two of the study investigators (JKS, CNC). If any differences in opinion occurred, they were resolved by consensus with a third reviewer.

Data extraction and management

Data were independently extracted by one unmasked reviewer (JKS) using a standardized electronic data collection form (based on the Cochrane Collaboration checklist of items to consider in data collection) [24]. When raw data were not provided, the data were extracted from figures; where necessary, we attempted to seek additional information from the first or corresponding authors of the included studies via electronic mail. The following information was obtained for each study (where possible): source, eligibility, methods, participants, interventions, outcomes, results, and funding sources. When possible, data from intention-to-treat (ITT) analysis were extracted; otherwise, we used the data presented on available cases.

Assessment of risk of bias in included studies

After identification of articles meeting the inclusion criteria, two review authors (CNC, JH) independently assessed the methodological quality of studies according to the "risk of bias approach" of the Cochrane Collaboration [25]. Specifically, we used the following six separate criteria:

- Adequate sequence generation (method of randomization)
- Allocation concealment
- Blinding of participants, personnel, and outcome assessors
- Incomplete outcome data addressed
- Free of selective reporting
- Free of other potential threats to bias/validity.

These criteria, which reflect the internal validity of the trials, were assessed for each of the included studies and were presented in a two-part "risk of bias" table. Within each entry, the first part of the tool involves describing what was reported in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry with each criterion scored as "yes," "no," or "unclear." This was achieved by answering a prespecified question about the adequacy of the study in relation to the entry such that a judgment of "yes" indicates low risk of bias, "no" indicates high risk of bias, and "unclear" indicates unclear or unknown risk of bias (see Appendix 2: The Cochrane Collaborations Risk of Bias Tool). Studies that met all criteria, or all but one criteria, were considered to be of high quality [25]. In the case of disagreement between reviewers, differences were to be resolved by discussion until consensus was achieved.

Measurement of treatment effect

A priori, we planned that for continuous data reported as means with standard deviations (SD), the effect measures would be generated as a mean difference (MD) or as a standardized mean difference (SMD) with 95% confidence intervals (CI). Specifically, for data measured on the same scale (i.e., a 10-cm or 100-mm VAS), a MD and the 95% CIs were calculated. When different methods of pain measures were used (i.e., a 10-cm VAS and a five-point pain scale), we calculated the SMD and 95% CIs to pool the results across trials. The SMD is used as a summary statistic in meta-analyses when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure pain but they use different scales). In this circumstance, it is necessary to standardize the results of the studies to a uniform scale before they can be combined. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study [26].

Where appropriate, data for dichotomous outcomes were pooled using the Mantel–Haenszel approach to calculate a risk ratio (RR) with 95% CIs. Numbers needed to treat for an additional harmful outcome (NNTH) were calculated for the reported side effects using the pooled RR and the assumed control risk (ACR) using the method described in Chapter 12.5.4.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* [27].

Dealing with missing data

As missing data (statistics) were evident in many of the included trials, we attempted to contact the trial investigators at least twice. In all but three cases, there were no responses; therefore, the available data were extracted from the published report and missing data were imputed. When only p values or the standard error of the mean (SEM) were reported, SDs were calculated according to the approach described in Chapter 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* for handling missing data [24]. Sensitivity analyses were performed to check the effect of imputation.

Assessment of heterogeneity and reporting bias

Heterogeneity between studies was described non-statistically and statistical heterogeneity between studies was examined visually using an I^2 statistic and a chi-squared test (a chi-squared p value of <0.1 or an I^2 value equal to or >50% was considered indicative of possible heterogeneity). Deeks and colleagues (for the Cochrane Collaboration) [27] suggest the following as a rough guide for interpreting the I^2 statistic:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Possible sources of heterogeneity were assessed by sensitivity analyses. Heterogeneity was also examined qualitatively and described in Table 1 (characteristics of included studies) and Table 2 (risk of bias in included studies). We planned to explore publication bias and other potential reporting biases using funnel plots [28].

Data synthesis

Meta-analyses were performed using the Cochrane Collaboration software program Review Manager (Rev Man), version 5 [29]. Meta-analyses methods were selected based on study heterogeneity and the number of trials included in the analyses. When the I^2 statistic

Table 1 Characteristics of included studies

Author (year) and country	Design	Study population			Intervention		Outcomes (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age (years) and sex	Treatment group	Control group	
Acute pain							
Arinoviche (1986) Chile	RCT, DB, PC Duration 14 days	32	Community	70 years; 29 females 3 males	*n*=15 Synthetic salmon calcitonin 100 IU SQ injection daily	*n*=17 Identical SQ placebo injection	Outcomes assessed at baseline, days 3, 7, and 14 •Pain with mobility (0 = none to 5 = pain in bed without moving) •Functional capacity (0 = no problem with everyday activities to 3 = maximum) •Global effectiveness (0 = no problems with everyday activity to 3 = impossible due to pain) •Number of paracetamol tabs and side effects were reported in each group daily
Levernieux (1986) (includes Attali 1986 and Bordier 1986)	RCT, DB, PC Duration 28 days	34	Community	71 years All female	*n*=15 Salmon calcitonin 50 IU IM or SQ injection daily	*n*=17 Placebo injection of identical form daily	Outcomes assessed at baseline, days 14, and 28 •Pain assessed by a 10 cm VAS (0 = no pain to 10 = intolerable pain) •Biochemical markers for bone turn over and BMD
Lyritis (1999) Greece	RCT, DB, PC Duration 28 days	40	Hospital	Ages 63–91 years 28 female 12 male	*n*=20 Synthetic salmon calcitonin 200 IU rectal suppository daily	*n*=20 Placebo rectal suppository daily	Outcomes assessed at baseline and then daily (reported weekly) •Pain assessed by a 10 cm VAS (0 = no pain to 10 = agonizing pain) during bed rest, sitting, standing, and walking, at the same time by the same observers •Pain assessed by a pain meter device (direct pressure on the fractured vertebra) in the same 4 positions (range 0–6) •Numbers of paracetamol tabs were reported in each group daily •Side effects recorded daily •Tolerability of calcitonin or placebo evaluated (3 = very good, 2 = good, 1 = poor, 0 = not tolerated) •Biochemical measurements done at baseline, days 14, and 28
Lyritis (1997) Greece	RCT, DB, PC Duration 28 days	100	Hospital	Female 71 years; males 76 years 68 female	*n*=50 Synthetic salmon calcitonin 200 IU IN daily	*n*=50 IN placebo daily	Outcomes assesses at baseline and daily •Pain assessment by VAS (0 = no pain to 10 = agonizing pain) every dayduring bed rest, sitting, standing, and walking

Table 1 (continued)

Author (year) and country	Design	Study population			Intervention		Outcomes (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age (years) and sex	Treatment group	Control group	
				32 male			•Side effects recorded daily •Tolerance of intervention reported (3 = very good, 2 = good, and 1 = poor)
Lyritis (1991) Greece	RCT, DB, PC Duration 14 days	56	Hospital	68 years All female	*n*=28 Synthetic salmon calcitonin 100 IU of IM injection daily	*n*=28 Placebo IM injection daily	Outcomes assesses at baseline and daily •Pain assessment by VAS (0 = no pain to 10 = agonizing pain) every day during bed rest, sitting, standing, and walking •Number of paracetamol tablets consumed reported in each group daily •Side effects recorded daily •Tolerance of intervention reported (3 = very good, 2 = good, and 1 = poor)
Pun (1989) Hong Kong	RCT, DB, PC Duration 28 days	18	Hospital	Age range 67–81 years 13 female 5 male	*n*=9 Synthetic salmon calcitonin 100 IU IN BID	*n*=9 Placebo IN	Outcomes assessed at rest and were initiated at baseline (on day 0) and then analyzed weekly on days 7, 14, 21, and 28 •Pain assessed with a VAS (0 = no pain and 10 = pain as bad as it could be) •Concurrent analgesics evaluated daily
Chronic pain (> 3 months duration)							
Abellan Perez (1995) Italy	RCT, no blinding, no placebo Duration 12 months	88	Community multicenter	63 years All female	*n*=43 Synthetic salmon calcitonin 100 IU IN for 14 days then 14 days off and then repeat pattern for 1 year and calcium 500 mg daily for 1 year	*n*=45 Calcium 1 g daily for 1 year, no placebo	Outcomes reported at baseline, 3, 6, 9, and 12 months •Pain scale with mobilization (1 = normal to 4 = movement impossible due to pain) •Analgesic consumption weekly (1 = null to 5 = more than 1 a day) •Self-reported pain scale (1 = absent to 4 = intense) •Drug tolerance and side effects reported daily
Consoli (1991) Italy	RCT, DB, PC Duration 6 months	20	Community	Treatment group 70 years, control group 61 years All female	*n*=10 Synthetic eel calcitonin IN 80 MRCU daily	*n*=10 Placebo nasal spray	Outcomes assessed at baseline and after 15, 30, 60, 90, and 180 days of treatment •Pain intensity at rest (0 = absent to 3 = very severe) •Daily analgesic consumption •Possibility of ADLs (0 = bed-bound to 3 = normal) •Compliance to treatment
Ljunghall (1991) Sweden	RCT, PC, DB Duration 4 months	60	Community female	Aged 58–82 years All	Group 1: *n*=20 Synthetic human calcitonin 0.25 mg SQ injection	*n*=20 Placebo injection 3 times a week	Outcomes assessed at baseline and after 1 and 4 months

					3 times a week Group 2: *n*=20 Synthetic human calcitonin 0.125 mg SQ injection 3 times a week		•Self-reported pain intensity measured on a 100-mm VAS (reported only at 1 and 4 months—baseline results were not provided) •Side effects were assessed monthly
Papado-kostakis (2006)	Open clinical trial. Randomized, no blinding, no placebo Duration 3 months	40	Community	Treatment group 65 years; control group 66 years All female	*n*=20 Synthetic salmon calcitonin 200 IU IN daily and 1000 mg of calcium daily	*n*=20 Calcium 1000 mg daily (no	Outcomes assessed at baseline and at 3 months (the end of the trial) •Pain intensity using an 11-point numerical rating scale (NRS) (0 = no pain and 10 = the most severe pain) •Functional status measures using the Oswestry disability questionnaire •Compliance evaluated by a telephone call monthly
Peichl (1999) Austria	Open, RCT, no placebo Duration 12 months	42	Community	63 years All female	*n*=24 Synthetic salmon calcitonin 200 IU IN daily for 2 months, then a 2 month pause over a total of 12 months (3 cycles) AND calcium 500 mg daily	*n*=18 Calcium 500 mg and vitamin D 400 IU daily for 12 months, no placebo	Outcomes measured at baseline and at the end of the trial (12 months) •Pain assessed on a 10-cm VAS (0 = no pain and 10 = unbearable pain) •Side effects recorded
Pontiroli (1994) Italy	RCT, DB, DP. Duration 4 weeks	28	Community	Age range 49–65	Group 1: Synthetic salmon calcitonin 200 IU IN daily AND IM placebo, *n*=9, (analyzed 8) Group 2: Synthetic salmon calcitonin 100 IU IM injection daily AND IN placebo, *n*=10, (analyzed 8)	Placebo IN AND placebo IM injection, *n*=9, (analyzed 8)	Outcomes assessed by the same physician at baseline and again on days 7, 14, 21, and 28 (weekly) •Pain score was measured by a VAS (0–100 mm—scores not defined) •VAS results presented as means with SEM
Szejnfeld (1991) Brazil	RCT, DB Duration 6 months	33	Community	65 years All female	*n*=16 Synthetic salmon calcitonin 100 IU IM during 5 days of the first 2 weeks of each month AND 1 g of calcium and 400 IU vitamin D daily	*n*=17 Placebo IM injection for the first 5 days of 2 weeks of each month AND 1 g of calcium and 400 IU vitamin D daily	Outcomes assessed at baseline and every 2 weeks until 24 weeks (6 months) •Pain intensity using a 10-point numerical scale (0 = no pain and 10 = maximum pain) •Functional capacity: ability to dress, walking capacity, and ability to climb or descendstairs (0 = no difficulty and 3 = maximum difficulty). The final value is in the sum of the values obtained in each of the items surveyed, with a maximum possible value of 9 •Side effects •Amount of analgesics used

DB double blind, *DP* double placebo, *ITT* intention to treat, *IM* intramuscular, *OP* osteoporosis, *PC* placebo controlled, *RCT* randomized controlled trial, *SD* standard deviation, *SQ* subcutaneous, *VAS* visual analogue scale

Table 2 Risk of bias in included studies (methodological quality summary)

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Acute pain (onset <10 days post fracture)						
Arinoviche (1986)	Unclear	Unclear	Yes	Yes	Yes	Unclear
	Quote "randomized according to a randomization list"	No information; comment: may have not been done	Described as DB, PC study. Placebo IN administered in the exact method as the TG	3 patients in the CG and 5 patients in the TG noted SE, 3 patients from the TG discontinued the study due to reported SE—not included in the sample sizes reported	All of the studies specified patient outcomes have been reported on	Insufficient information to assess whether an important risk of bias exists
Levernieux (1986)	Unclear	Unclear	Yes	No	Yes	Unclear
	Described as "randomized" but not defined	No information. Comment: may have not been done	Described as DB, PC study. Placebo IM injection administered in the exact method as the treatment group	Two patients from the TG did not complete the study and were excluded from the results	All of the studies specified patient outcomes have been reported on	Insufficient information to assess whether an important risk of bias exists. This study was described in 3 separate publications
Lyritis (1999)	Yes	Yes	Yes	Yes	Yes	Yes
	Quote "prospective, DB, randomized, PC clinical trial". Method of randomization not described in the publication but author reports adequate sequence generation procedures	The ordering of the cards within the envelopes was determined from a table of random numbers	Quote "DB". Suppositories administered by a nurse at the same time every day	4 withdrawals: 1 from the TG because of enteric disturbances, and 3 from the CG: 2 because more potent analgesics needed, 1 at his own request	All of the studies specified patient outcomes have been reported on	The study appeared to be free of other sources of bias
Lyritis (1997)	Yes	Yes	Yes	Yes	Yes	Yes
	Quote "prospective, DB, randomized, PC clinical trial". Method of randomization not described in the publication but author reports adequate sequence generation procedures	The ordering of the cards within the envelopes was determined from a table of random numbers.	Quote "…assigned to receive either salmon calcitonin IN 200 IU or a matching placebo IN". Patients in hospital and received IN spray from a nurse	No withdrawals or dropouts	All of the studies specified patient outcomes have been reported on	The study appeared to be free of other sources of bias
Lyritis (1991)	Yes	Yes	Yes	Yes	Yes	Yes
	Quote "prospective, DB, randomized, PC clinical trial". Method of randomization not described in the publication but author reports adequate sequence generation procedure	The ordering of the cards within the envelopes was determined from a table of random numbers	Quote "…salmon calcitonin or placebo injections…" Patients in hospital and received injections from a nurse	No withdrawals or drop outs	All of the studies specified patient outcomes have been reported on	The study appeared to be free of other sources of bias

Pun (1989)	Yes Quote "randomized according to a table of randomized numbers"	Unclear No information; comment: may have not been done	Yes Quote "…received salmon calcitonin IN twice a day…or placebo containing only carrier"	Unclear Withdrawals and dropouts not described. Side effects not mentioned	Yes All of the studies specified patient outcomes have been reported on	Unclear Insufficient information to assess whether an important risk of bias exists
Chronic pain (>3-month duration)						
Abellan Perez (1995)	Unclear Quote "numerous randomized blocks of two". Comment: probably done	Unclear No information; Comment: may have not been done	No Comment: CG administered only calcium; no placebo IN preparation. Assume that blinding was not done as it was not directly mentioned	Yes 1 patient discontinued in the TG due to side effects of the drug. No missing outcome data	Yes All of the studies specified patient outcomes have been reported on	Unclear Insufficient information to assess whether an important risk of bias exists
Consoli (1991)	Unclear Quote "randomized, DB clinical trial"; randomization not described	Unclear No information. Comment: may have not been done	Yes Quote "…DB clinical trial"	Yes All patients completed the trial and all reported on	Yes All of the studies specified patient outcomes have been reported on	Yes The study appeared to be free of other sources of bias
Ljunghall (1991)	No Quote "randomly allocated in equal numbers to each of the three groups" Randomized in blocks of 3	Unclear No information. Comment: may have not been done	Yes Quote "PC". Three groups self administered the drug/placebo in the same method with identical syringe	Yes All patients completed the trial and all reported on	Unclear Self reported pain intensity measured on a 100-mm VAS (reported only at 1 and 4 months—baseline results were not provided)	Yes The study appeared to be free of other sources of bias
Papado-kostakis (2006)	Yes Quote "block (or restricted) randomization was used." Quote "randomly assigned in 1:1 ratio"	Unclear No information. Comment: may have not been done	No No placebo, patients received either calcitonin by injection and calcium or just calcium	Yes Two patients discontinued the calcium treatment but ITT analysis done	No Incomplete description of outcomes for one of the groups	Unclear Insufficient information to assess whether an important risk of bias exists
Peichl (1999)	Yes Quote "…open randomized study". Methods of randomization not described	Unclear No information. Comment: may have not been done	No Open study with no placebo, patients received either IN calcitonin and calcium or just calcium and vitamin D	Yes No description or mention of withdrawals or dropouts	Yes All of the studies specified patient outcomes have been reported on	Unclear Insufficient information to assess whether an important risk of bias exists
Pontiroli (1994)	Unclear Quote"…randomly allocated to one of 3 groups". Methods of randomization not described	Unclear No information. Comment: may have not been done	Yes Described as DB with double placebo and a PC group	Yes Dropouts were described and were equal in all 3 groups	Yes All of the studies specified patient outcomes have been reported on	Yes The study appeared to be free of other sources of bias
Szejnfeld (1991)	Unclear Quote "…randomized, DB study"	Unclear No information. Comment: may have not been done	Yes Quote "DB". Patients received an injection (calcitonin or placebo) and calcium and vitamin D	Yes 4 dropouts in PG due to SE—ITT analysis done	No Did not report VAS scores for weeks 6, 10, 14, 18, or 22	Unclear Insufficient information to assess whether an important risk of bias exists

CG control group, *DB* double blind, *DP* double placebo, *IN* inter nasal, *ITT* intention to treat, *IM* intramuscular, *OP* osteoporosis, *PC* placebo controlled, *RCT* randomized controlled trial, *SD* standard deviation, *SE* side effects, *SQ* subcutaneous, *TG* treatment group, *VAS* visual analogue scale

was >75%, we considered it substantial heterogeneity and pooled the study results using a random effects (RE) model. If no significant statistical heterogeneity was detected, or there were a small number of trials included in the analysis (three or fewer), we used a fixed-effect model [27].

Continuous data were entered into Rev Man in such a way that, when analyzing the forest plot graphs, the area to the left of midline (<0) indicated a positive effect of the treatment drug calcitonin. When interpreting results of the forest plots for dichotomous data, the area to the right side of the forest plot graph (>1) favored the control group.

Subgroup analysis and investigation of heterogeneity

A priori, we planned to explore and address possible clinical heterogeneity as well as to investigate the effect modification of participants and treatments by performing subgroup analyses on the route of calcitonin administration (IN, IM/SQ, or rectal), the synthetic derivative of calcitonin (salmon vs. eel. vs. human), and the efficacy of calcitonin for both acute (<10 days) and chronic pain (>3 months). For studies examining acute fracture pain, we defined five periods for which we tried to extract data and analyze study findings: baseline, week 1, week 2, week 3, and week 4. For studies examining chronic pain of remote fractures, we aimed to extract data and analyze study findings at baseline and then again at 1, 3, 6, 9, and 12 months.

Sensitivity analysis

We performed sensitivity analyses by examining the results of the meta-analysis under different assumptions and checked for the robustness of the observed findings. A priori, the following sensitivity analyses were planned:

1. For trials in which the SD was not reported and therefore had to be imputed, do the results of the pooled analysis change if these are excluded from the results?
2. By limiting included studies in the analyses to those with the highest methodological quality, do the results change?

Results

Figure 1 outlines the study selection process. We initially identified 308 citations, of which 55 were potentially relevant studies. Of the 55 full text articles retrieved for closer examination, 42 were excluded for the following reasons: 11 included patients with no vertebral fracture [20, 30–39], nine had insufficient data and we were unable to locate study authors [40–48], six had a diagnosis other than osteoporosis [49–54], six lacked an inactive (or no drug) comparison group [55–60], the library was unable to locate three full text articles and we were unable to locate the study authors [61–63], three were review articles [64–66], two were duplicate publications from a single study reporting the same results [67, 68], one was a case report [69], and one included participants with multiple fracture sites [70]. Thirteen trials were identified which met the inclusion criteria for the systematic review; six were studies focused on the acute pain of recent fractures [71–76] and seven were chronic pain studies [16, 17, 77–81]. We were unable to include three of the studies in the meta-analysis due to insufficient data (means and SD of pain score not provided) [17, 76, 78]. Therefore, 10 studies were included in the quantitative synthesis.

Characteristics of included studies

Participants

The 13 included studies involved 589 participants, all of whom contributed data to the withdrawal and side effect analyses; 10 studies with 467 participants provided data in the analgesic efficacy (pain scale) meta-analyses. Recruitment procedures were predominantly not defined or were poorly reported, with little detail provided; however, it appeared that convenience samples predominated. See characteristics of included studies in Table 1.

Design

All studies included were randomized, prospective controlled trials; most of the trials described withdrawals and side effects. Three of the trials were randomized and double-blinded [73–75] with the use of sealed, serially numbered opaque envelopes. As patients met the appropriate criteria and became eligible for entry into trial, the next in a pile of sealed envelopes was opened. Inside was a card that indicated whether the patient was assigned to the treatment or control group. The ordering of the cards within the envelopes was determined from a table of random numbers. An additional three of the studies utilized "block randomization" [16, 17, 78]: One of the trials was randomized according to a "randomization list" [71], one randomized participants according to a table of randomized numbers [76], and the remaining five studies simply stated that they randomized participants, but did not describe their methods [17, 72, 77, 79, 80].

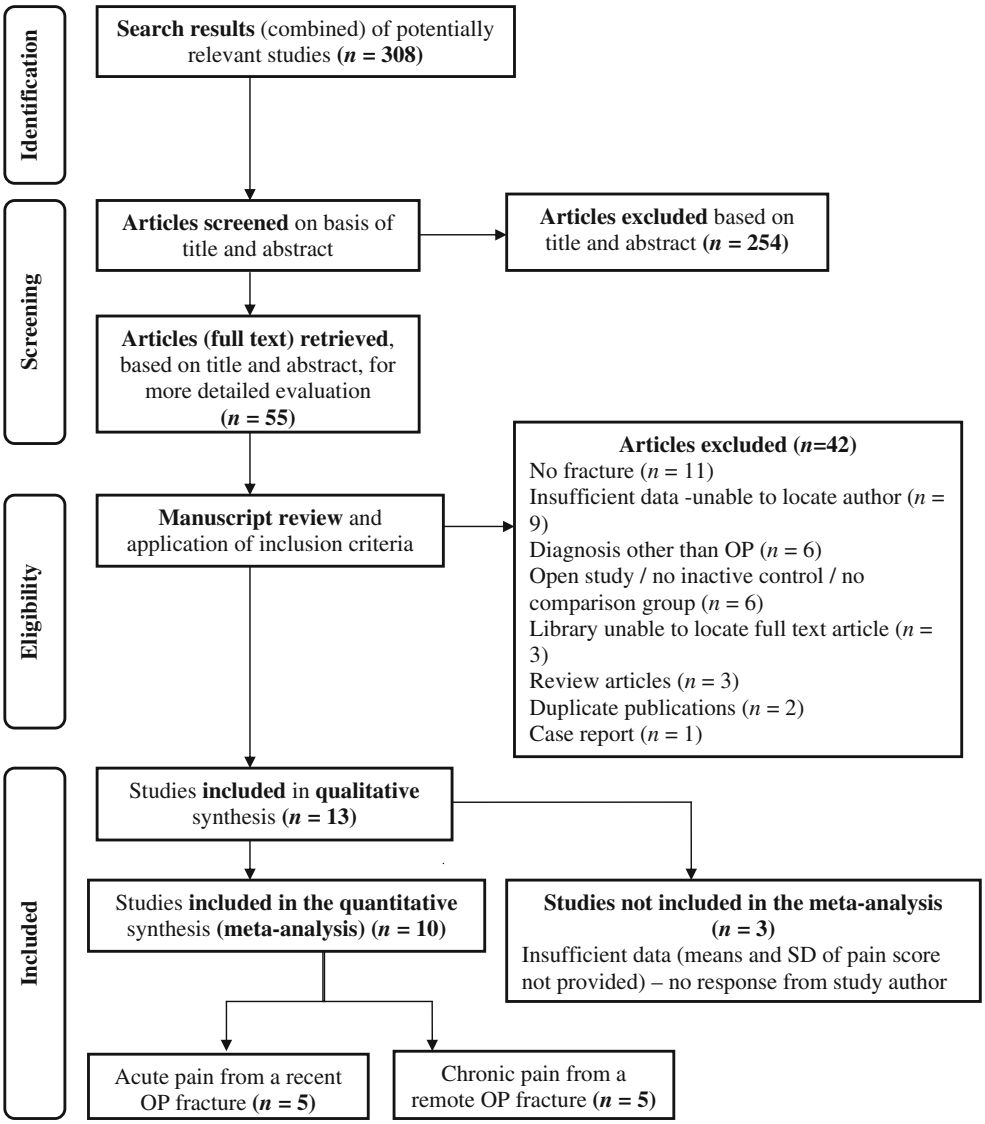

Fig. 1 Flow diagram of study selection

Setting

A single research group in Greece conducted three of the studies [73–75] and three of the studies were conducted in Italy [16, 77, 80]; the remaining studies were conducted in Austria [79], Brazil [81], Chile [71], France [72], Greece [78], Hong Kong [76], and Sweden [17]. Four of the studies were conducted using hospitalized patients [73–76]; the remaining nine studies included participants from the community. Only one of the studies was a multicentre trial [16].

Interventions

The intervention groups received calcitonin by various routes: either nasal spray (seven studies) [16, 74, 76–80], injection (six studies) [17, 71, 72, 75, 80, 81], or by rectal suppository (one study) [73]. Ten studies included an identical placebo group [17, 71–77, 80, 81], and three studies included a comparison group where the participants received various doses of calcium and vitamin D, but did not receive a placebo [16, 78, 79].

Outcomes

Of the 13 studies included, six involved patients with acute back pain (<10 days) attributed to a recent OVCF [71–76] and seven included patients with chronic back pain (>3 months) attributed to a remote OVCF [16, 17, 77–81]. Although all studies analyzed pain scores, three studies presented their data in such a way that the results could not be included in the meta-analysis [17, 76, 78]. The timing of outcome measures was variable, ranging from 14 to 28 days for measures of acute pain and from 1 week to 1 year for measures of chronic pain. Various pain scales were used in

the trials: a 10-cm or 100-mm VAS predominated (0 = no pain to 10 = intolerable pain) [17, 72–76, 78–81], followed by studies utilizing a descriptive four-point scale (0/1 = normal to 4 = movement impossible/very severe) [16, 77] and a five-point scale (0 = none to 5 = pain in bed without moving) [71]. All studies provided information on withdrawals and side effects experienced by both treatment and comparison groups. With the exception of the participants in one of the studies [80], all participants were allowed concomitant analgesics, but only a few of the studies provided data on their usage.

Quality assessment—risk of bias in included studies

The methodological quality of trials varied significantly (see summary results presented in Table 2). The initial agreement of the reviewers on the total assessment of risk of bias was 97% (74 of 76 items). Any initial disagreements were solved by consensus. An adequate method of sequence generation was reported in five trials [73–76, 78] and an adequate method for allocation concealment in three trials [73–75]. Patients were blinded in all but three studies [16, 78, 79], and attrition was low or adequately accounted for in all but one study [72]. Three studies met all formal quality criteria [73–75], one study met four criteria [80], and four studies met three of the quality requirements [17, 71, 76, 77]. A priori, publication bias was to be tested using the funnel plot visually and quantitatively, that is, the rank correlation test [82] and the graphical test with or without heterogeneity [28]. However, given the small number of trials included in the review, the interpretation of these plots must be undertaken with caution and are not included here.

Effects of interventions: analgesic efficacy of calcitonin

The statistical analysis (related to the analgesic efficacy of calcitonin) included data from 10 trials with 467 participants [420 women (90.0%) and 47 men (10.0%)]. The mean ages of participants (at entry) in the treatment and control groups were 67.4 and 66.9 years, respectively. The studies were analyzed and the results pooled for two separate groups: those including participants with (1) acute back pain (<10 days duration) [71–75] attributed to a recent OVCF and (2) chronic back pain (>3 months duration) [16, 77, 79–81] attributed to a remote OVCF.

Acute back pain

Five studies included participants with acute back pain of a recent OVCF [260 participants, 213 females (82%) and 47 males (18%)]. The mean age of participants was 70.8 years in the calcitonin group and 71.2 years in the control group. Of the five studies, three used a 10-cm VAS [73–75], one used a 100-mm VAS [72], and the final used a descriptive five-point scale as a subjective measure of participant self-reported pain [71]. In three of the trials, VAS measures were initiated on day 0 (baseline) and then again at least weekly for up to 4 weeks during bed rest, sitting, standing, and walking [73–75]. Another study measured pain scores with patients only at rest and assessed pain on a 100-mm VAS at baseline, week 2, and again at week 4 [72]. The final study measured pain by assessing patients' activity/mobility using a five-point scale; the measurements were assessed at day 0 (baseline) and days 3, 7, 14, 21, and 28 [71].

As determined a priori, two subgroups were created: (1) pain assessed at rest and (2) pain assessed with mobility. Because there were too few trials and insufficient data, we were unable to carry out subgroup analysis based on sex and age of participants or the route of calcitonin administration. Within the subgroups, analyses were done at baseline and then weeks 1 to 4. All five of the studies employed the use of salmon calcitonin; therefore, sensitivity analysis related to calcitonin derivative was not necessary. Overall, a small number of trials were included and the pooled analyses displayed statistical heterogeneity; therefore, the estimates were based on the RE model [27].

Acute pain at rest Four trials studied participants while at rest or stationary [72–75]; baseline results of the population revealed a relatively homogeneous sample with moderate to severe pain (VAS ranged from a mean score of 6.1 to 10 out of 10) with no statistical difference between the groups (p=0.56). Following 1 week of treatment, there was a statistically significant improvement in the resting pain score for patients receiving calcitonin (MD=−3.39, 95% CI=−4.02 to −2.76) compared with the control group. The chi-square test of heterogeneity was not significant for the RE pooled result (I^2=24%, p=0.27). This result was not significantly different from the results seen at 2, 3, and 4 weeks with the subjects at rest (forest plot of the results presented in Fig. 2).

Significant heterogeneity (I^2>90%) of the RE pooled results (with participants at rest) was demonstrated in weeks 2 and 4. Sensitivity analyses, based on the imputing of SDs where means were provided (but no SD) [72, 73], were non-significant as the direction and magnitude of treatment effect did not change. For example, the VAS (pain scores) measured at rest on week 2, excluding the studies with no SD provided, showed a homogeneous sample (I^2=0%) with a MD of −4.65 (95% CI=−5.18 to −4.12) as compared with a MD of −3.75 (95% CI=−5.52 to −1.98) when including all four studies.

Acute pain with mobility Four trials studied participants while mobile [71, 73–75]; baseline results of the population revealed a homogeneous sample (I^2=18%, p=0.30) with no

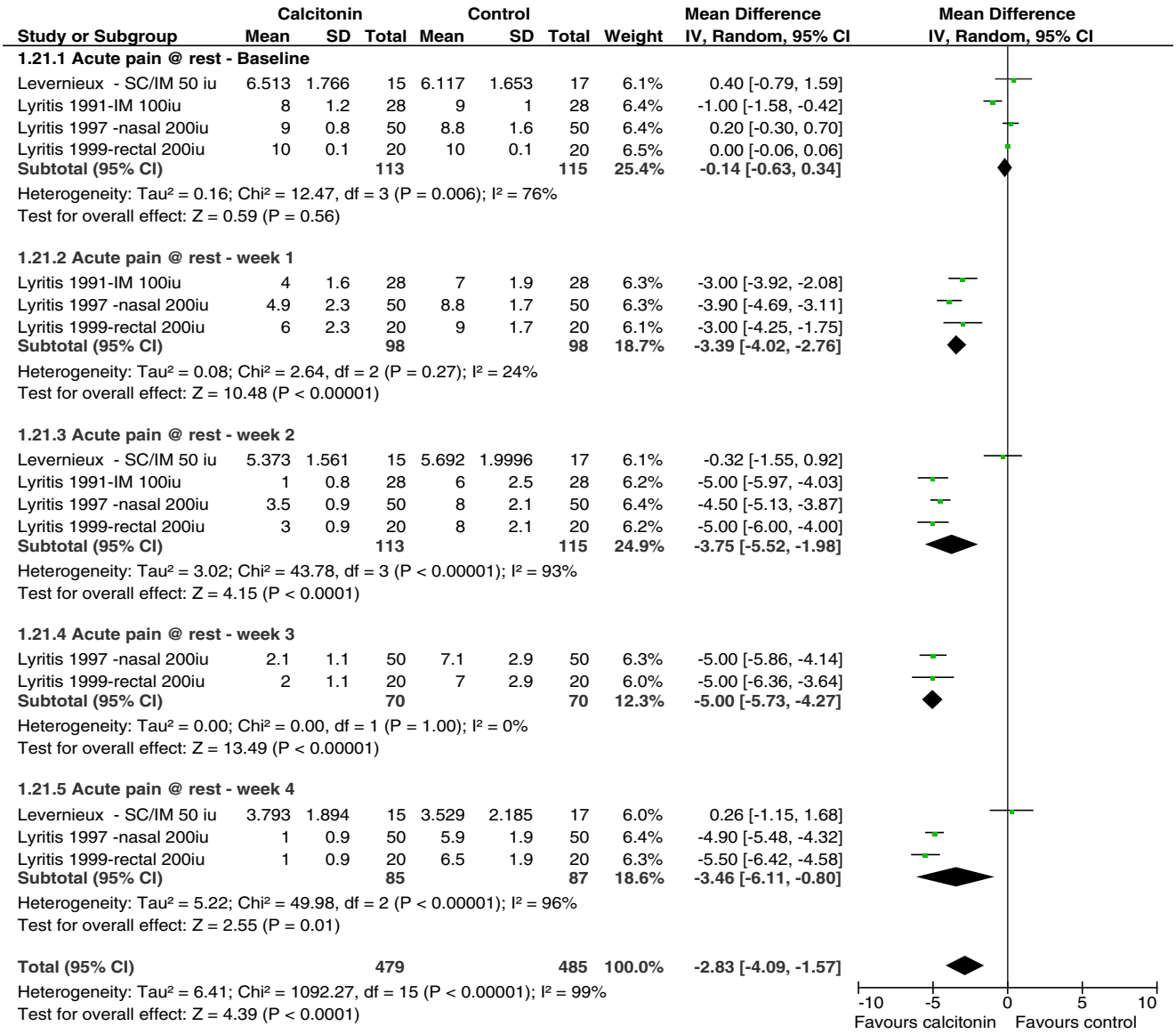

Fig. 2 Acute pain measured at rest. Forest plot of all included studies reporting the acute pain of a recent OVCF, measured at rest on day 0 (baseline) and weeks 1 to 4. *Horizontal lines*, 95% CIs of each study; *green squares*, MDs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the summary estimate; solid vertical line, null value. MDs less than zero indicate a treatment benefit

statistical difference between the groups (p=0.46). By week 1, there was a significant improvement in the RE pooled score (SMD=−2.60, 95% CI=−4.07 to −1.13) compared with the control group. This result was not significantly different from results seen at weeks 2, 3, and 4 (forest plot of the results presented in Fig. 3).

The only comparisons demonstrating significant heterogeneity in their RE pooled results were at weeks 1 and 2 (I^2>90%). Sensitivity analyses, based on the imputing of SDs into the studies where means were provided (but no SD) [71, 73], were non-significant as the magnitude of the treatment effect did not change. For example, the pain scores with mobility at week 2, excluding the studies where the SD was imputed, showed a SMD of −4.35 (95% CI=−6.23 to −2.47) as compared with a SMD of −3.75 (95% CI=−5.52 to −1.98).

Chronic back pain

The five studies including participants with chronic back pain of a remote OVCF included 207 participants (100% women). The mean age of participants was 64 years in the calcitonin group and 63.1 years in the control group. Of the five studies, two used a 10-cm VAS [79, 81], one used a 100-mm VAS [80], and two used descriptive four-point scales as a

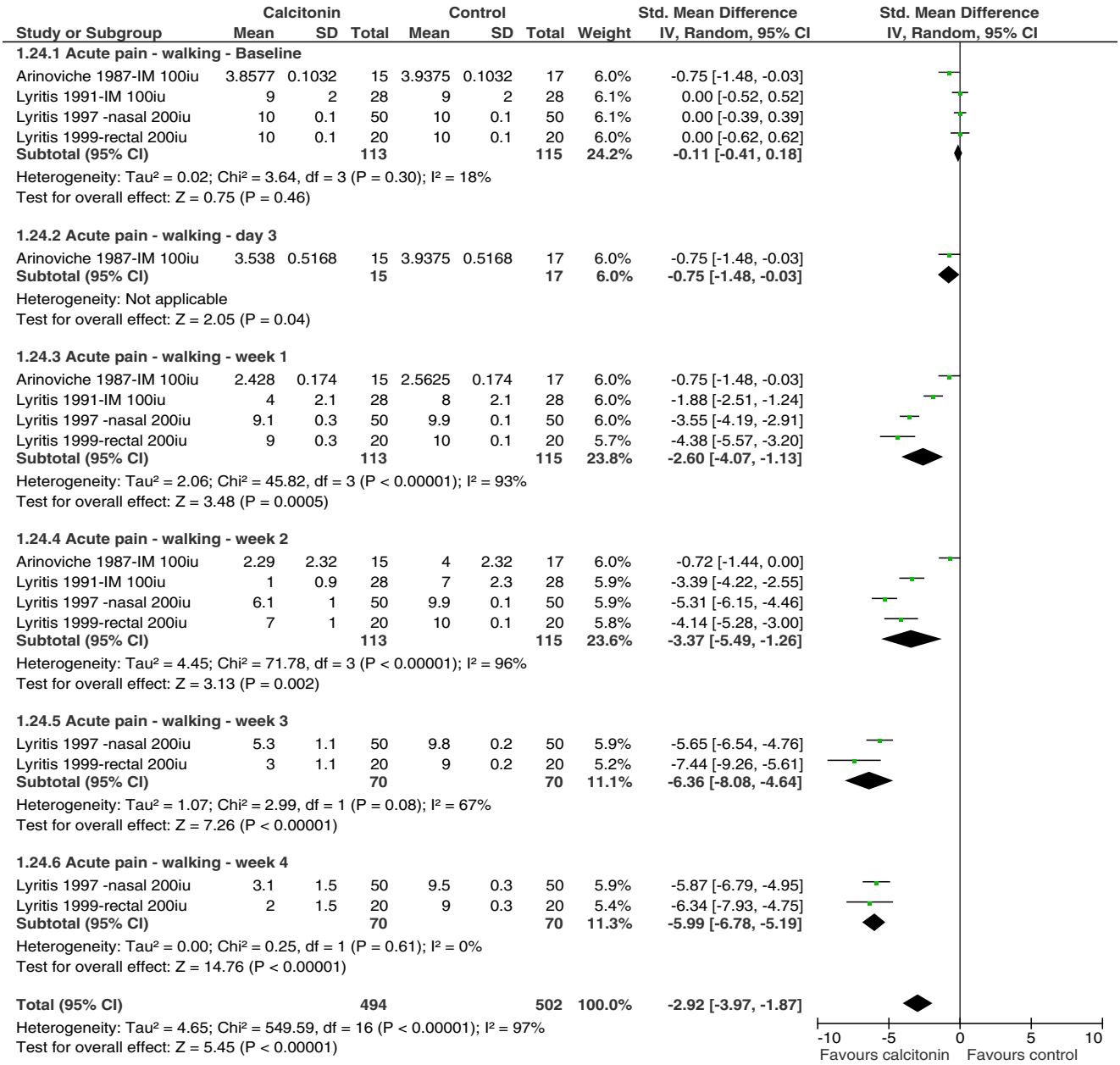

Fig. 3 Acute pain measured with activity/walking. Forest plot of all included studies reporting the acute pain of a recent OVCF, measured at while mobile on day 0 (baseline) and weeks 1 to 4. *Horizontal lines*, 95% CIs of each study; *green squares*, SMDs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the summary estimate; solid vertical line, null value. SMDs less than zero indicate a treatment benefit

subjective measure of participant self-reported pain [16, 77]. All of the trials initiated pain score measurements at baseline (day 0), one of the trials followed patients closely for 6 months [81], and two of the trials followed patients for up to 1 year [16, 79]. The remaining two trials employed short-term measures: One assessed pain scores weekly for up to 4 weeks [80] and the other assessed patients at 2 weeks and then monthly for 3 months [77].

As determined a priori, two subgroups were created: (1) pain assessed at rest and (2) pain assessed with mobility. Because there were too few trials and insufficient data, we were unable to carry out subgroup analysis based on sex and age of participants or the route of calcitonin administration. For pain assessed at rest, pooled analyses were only possible at baseline and then at 3 months. For the group assessed while mobile, pooled analyses were possible at baseline, weekly until week 4, and then again at 3 and 6 months. Overall, there were a small number of trials included and the pooled analyses displayed statistical heterogeneity; therefore, the estimates were based on the RE model [27].

Chronic pain at rest Two of the five studies included assessments while patients were at rest [16, 77]. The baseline result of this chronic back pain population revealed a homogeneous sample (I^2=0%, p=0.36) with slight statistical difference between the groups (p=0.01). After 3 months of treatment, there were no statistically significant improvements in the resting pain scores for patients receiving calcitonin (SMD=0.17, 95% CI=−1.46 to 1.12) compared with the control group. The chi-square test for heterogeneity was relatively significant for the RE pooled result (I^2=84%, p=0.01). One study reported results for up to 1 year [16], with no statistically significant difference in pain scores between the calcitonin group and the control group (SMD=−0.42, 95% CI=−0.84 to 0.00, p=0.05).

Sensitivity analysis, based on the imputing of SDs into the studies where means were provided (but no SD), was not done as the SD had to be imputed for both of the included trials. Of the two included studies, one used synthetic eel calcitonin [77] and the other synthetic salmon calcitonin [16]; with limited data provided, sensitivity analyses related to calcitonin derivative could not be done.

Chronic pain with mobility Four of the five studies measured chronic back pain with activity [16, 79–81]; RE pooled results of the population at baseline revealed a homogeneous sample (I^2=0%, p=0.44) with no statistical difference between groups (p=0.29). With the exception of the pooled results at 6 months, there were no significant improvements in pain scores. At 6 months, there appeared to be a significant difference in pain scores for the calcitonin group (SMD=−0.49, 95% CI=−0.85 to −0.13, p=0.008, I^2=0%) compared with the control group (forest plot of the results presented in Fig. 4).

The only comparisons demonstrating heterogeneity (I^2= 86%, p<0.0009) in their RE pooled results was at 3 months. As SD for both of the studies reporting results at 3 months were not provided (and were therefore imputed) [16, 81], sensitivity analysis was not done.

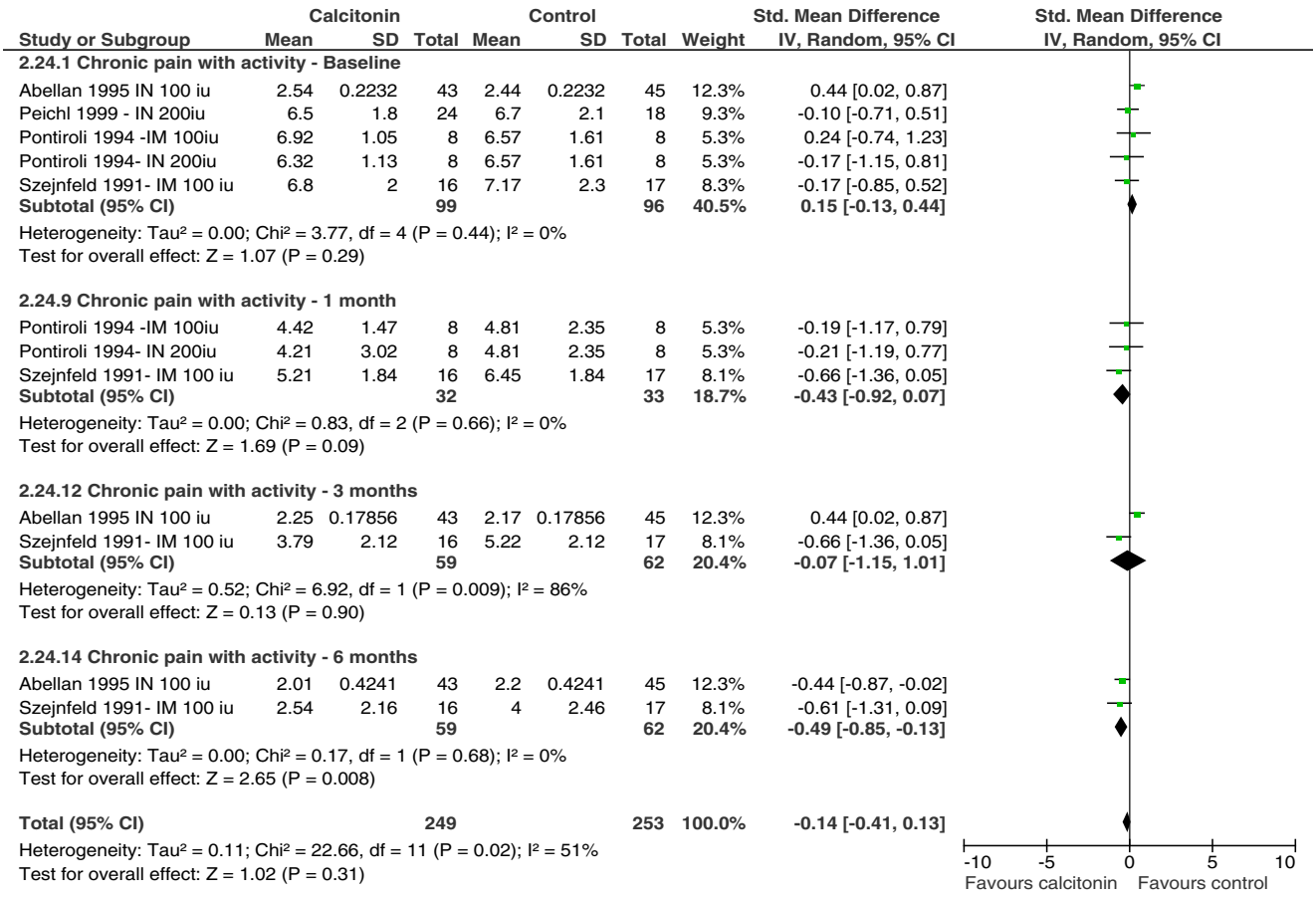

Fig. 4 Chronic pain measured with activity. Forest plot of all included studies reporting chronic pain of a remote OVCF, measured while mobile on day 0 (baseline), week 1 to 3, and months 1, 2, 3, 6, 9, and 12. *Horizontal lines*, 95% CIs of each study; *green squares*, SMDs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the summary estimate; solid vertical line, null value. SMDs less than zero indicate a treatment benefit

Effects of interventions: withdrawals and side effects

Of the 13 studies included in the review, all provided information on withdrawals and side effects (n=589 participants); data were stratified by route of calcitonin administration [IN, injection (IM or SQ), and rectal].

Withdrawals

Of the 13 included studies, six reported 16 patient withdrawals; nine (7.2%) withdrawals were from the calcitonin group (eight due to side effects and one with no reason provided) and seven (5.3%) from the control group (one related to side effects, five due to lack of efficacy, and one with no reason provided). The pooled RE model provided a RR of 1.26 (95% CI=0.46 to 3.43), and the calculated number needed to treat to prevent one additional withdrawal (NNTH) for all cause withdrawal was 73. Specifically, two studies, both examining chronic pain, reported two withdrawals from the IN calcitonin group (3.9%) and none from the control group, giving a RR of 3.07 (95% CI=0.34 to 27.79, p=0.32). Four studies using injectable calcitonin (IM or SQ), two of which reported on acute pain and two on chronic pain, reported six (11.1%) withdrawals from the calcitonin group and four (6.8%) from the control group; the RE pooled analysis showed a RR of 1.49 (95% CI=0.40 to 5.61, p=0.55) and a calculated NNTH of 30. One study utilizing rectal suppository calcitonin reported one withdrawal (5%) from the treatment group and three (15%) withdrawals from the control group; this was not statistically significant (p=0.32; see Table 3).

Side effects

The 13 included studies reported 104 separate side effects; 85 were reported in the calcitonin group [the majority due to enteric disturbances (47%) and flushing (32%)] and 19 in the control group [mainly due to enteric disturbances (68%)]. The pooled RE model showed a RR of 3.09 (95% CI=1.80 to 5.32, p<0.0001) and a calculated NNTH of 12 (the number of patients who receive calcitonin that will lead to one additional patient experiencing a side effect, in comparison to the control group). Side effects were generally reported as mild, with the majority being either enteric disturbances (RR=2.58, 95% CI=1.10 to 6.04) or flushing (RR=6.91, 95% CI=2.47 to 19.36), both of which were statistically significant (see Table 4).

Concomitant analgesic use

We were not able to utilize statistical methods to assess concomitant analgesic use as there were not only substantial gaps in the data reported but also important differences in the

Table 3 Withdrawals from included studies

Route of administration	No. of studies	No. of patients		Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	p value[b]	NNTH[c]
		Control group	Calcitonin group	Assumed risk Control group Study population	Corresponding risk Calcitonin group			
Intranasal	2 (n=104)	0/53 (0%)	2/51 (3.9%)	0 per 1,000	0 per 1,000	RR 3.07 (0.34–27.79)	0.32	0[d]
Injection	4 (n=113)	4/59 (6.8%)	6/54 (11.1%)	68 per 1,000	103 per 1,000 (34–306)	RR 1.49 (0.4–5.61)	0.55	30
Per rectum - suppository	1 (n=40)	3/20 (15%)	1/20 (5%)	150 per 1,000	50 per 1,000 (6–441)	RR 0.33 (0.04–2.94)	0.32	10
Total withdrawals	7 (n=257)	7/132 (5.3%)	9/125 (7.2%)	53 per 1,000	68 per 1,000 (29–158)	RR 1.26 (0.46–3.43)	0.65	72

ACR assumed control risk, *CI* confidence interval, *NNTH* number needed to treat to prevent one withdrawal, *RR* risk ratio

[a] The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[b] p value is for the Z statistic

[c] $\mathrm{NNTH} = \frac{1}{\mathrm{ACR}\times(1-\mathrm{RR})}$

[d] Unable to estimate, no adverse reaction in the control group

Table 4 Side effects reported in included studies

Side effects	No. of studies	No. of patients		Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	*p* value[b]	NNTH[c]
		Control group	Calcitonin group	Assumed risk Control group Study population	Corresponding risk Calcitonin group			
GI/enteric	10 (n=381)	13/193 (6.7%)	40/188 (21.3%)	67 per 1,000	182 per 1,000 (109–304)	RR 2.52 (1.10–6.04)	0.03	9
Flushing	7 (n=305)	1/155 (0.6%)	27/150 (18%)	6 per 1,000	46 per 1,000 (17–128)	RR 6.91 (2.47–19.36)	0.0002	28
Dizziness/headache	2 (n=56)	2/28 (7.1%)	7/28 (25%)	71 per 1,000	213 per 1,000 (54–836)	RR 1.92 (0.10–36.81)	0.66	15
Ears, nose, throat	3 (n=74)	0/34 (0%)	5/40 (12.5%)	0 per 1,000	0 per 1,000[d]	RR 3.89 (0.70–21.66)	0.12	0[d]
Other, not specified	2 (n=132)	3/67 (4.5%)	6/65 (9.2%)	45 per 1,000	83 per 1,000 (24–288)	RR 1.45 (0.02–110.08)	0.87	49
Total side effects	12 (n=948)	19/477 (4.0%)	85/471 (18.1%)	40 per 1,000	136 per 1,000 (92–202)	RR 3.09 (1.80–5.32)	<0.0001	12

ACR assumed control risk, *CI* confidence interval, *NNTH* numbers needed to treat for an additional harmful outcome, *RR* risk ratio

[a] The assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Corresponding intervention risk, per 1,000=1,000 × ACR × RR

[b] $\mathrm{NNTH} = \frac{1}{\mathrm{ACR} \times (1-\mathrm{RR})}$

[c] p value is for the Z statistic

[d] Unable to estimate, no adverse reaction in the control group

reporting of results between studies. Seven studies reported analgesic use as an outcome of the study; this varied significantly from reporting the daily or weekly mean consumption of acetaminophen [16, 71, 73, 74, 77, 81] to converting the analgesic administered to equivalent milligrams of morphine ingested daily [76]. In five of the studies, concomitant analgesic use was not an outcome of interest and was therefore not reported on [17, 72, 75, 78, 79]; in one of the studies, concomitant analgesia was not permitted [80].

Discussion

Overall, the evidence presented in this review supports the use of calcitonin as an effective analgesic for the acute pain of recent OVCF in older adults. The included studies demonstrated a clear benefit with respect to pain relief. Pain was rated as severe by patients in both groups at baseline, suggesting that this diagnosis is important not only to health care providers but also to individual patients. By 1 week post-treatment, there were clinically (≥20/100 mm on the VAS) and statistically significantly differences in the pain scores of the calcitonin group compared with those in the control group. Various studies have investigated the minimum clinically significant change in patients' pain severity measured with a 10-cm VAS and found 1.3 cm as the cutoff [83, 84]. This, along with the finding that all studies of acute pain of OVCF reported statistically significant results for the analgesic efficacy of calcitonin, suggests that these results are not due to chance. Although not specifically evaluated in this review, earlier mobilization would be expected to reduce the incidence of other problems associated with immobility such as muscle atrophy and venous thromboembolism.

Although used in clinical practice, the findings of this review do not support the use of calcitonin for chronic pain of more remote OVCFs. The subgroup analysis of analgesic efficacy with patients at rest did not demonstrate any clinical or statistical difference in pooled results from baseline through year 1. For the pooled analyses of patients while mobile, there was statistical significance only at 6 months in pain scores for the calcitonin group compared with the control group; regardless, we did not determine this to be of clinical importance.

We postulated that the route of administration may have in part explained the heterogeneity of the results. Unfortunately, due to so few studies included in the individual analyses, it was not possible to do subgroup analysis based on route of calcitonin administration. For example, either there was only one study included per route of administration or the calcitonin was given in different doses (IM 50 vs. 100 IU), making it impossible to compare the results. The included studies used different routes of administration

and various doses of calcitonin; therefore, insufficient data were available to evaluate a dose–response effect of calcitonin. However, it appeared that the trials employing IM or SQ injections showed the greatest difference in pain scores between calcitonin and control groups. This may be in part due to the greater bioavailability of the drug when administered via the IM route. The bioavailability of IN calcitonin is only about 25% of the administered dose as compared with the injectable preparation, which is 70% bioavailable [85]. Clinically, given the age and comorbidities of the affected patients, it is clearly easier to administer the agent via the IN route than the IM route, adjusting the dose accordingly to reflect bioavailability of the drug.

The withdrawal rate for any cause was low and was seen in slightly more patients in the treatment group than placebo; this was not a statistically significant finding. The NNT to prevent one additional withdrawal (for all cause withdrawal) with calcitonin was high at 73. There were more withdrawals in the acute pain group than in the chronic pain group; this is not surprising as, presumably, the patients in these trials would have been suffering from acute, extreme pain and almost all of the withdrawals were due to lack of perceived efficacy (not side effects).

Overall, this treatment approach seems to be safe. There were side effects reported in these trials; however, they were generally described as mild and self-limiting. There were statistically significant increases in gastrointestinal/enteric disturbances and flushing compared with placebo. These side effects may in part be related to the route of administration as both were noticed predominantly in the studies where injectable calcitonin was utilized. There were also more side effects in the chronic pain group; given the much longer duration of these studies (1 year vs. 4 weeks), this was expected.

Overall completeness and applicability of evidence

There are several methodological issues that would limit the generalizability (external validity) of these results, although the overall findings seem to apply to all patients. Due to the small number of trials included in this meta-analysis and the overall small number of patients upon which these results are based, no firm conclusions regarding the subgroups (other than the acute pain group) can be made.

Four of the five studies included in the acute pain analysis were conducted in a hospital setting where patient presentations may be more severe than in an ambulatory office or clinic setting. Consequently, the results pertaining to the use of calcitonin for acute OVCF need confirmation in the community setting. In addition, the overall findings may only be generalized to people who have OVCF and limited comorbid disease as described in the exclusion criteria of the studies. People with secondary osteoporosis or those receiving concomitant osteoporosis treatments were not studied. Moreover, analyses adjusting for confounding factors or population stratification were not performed due to insufficient data.

Quality of the evidence

The methodological quality of the individual included studies was assessed according to the "risk of bias approach" of the Cochrane Collaboration [25]. Information related to acceptable randomization, allocation concealment, and blinded outcome assessments varied significantly and were not adequately reported in most of the studies. In fact, only three studies addressed all six of the formal quality criteria. Although the authors of the 13 included studies all claimed that their study design was a randomized controlled trial, an appropriate method of randomization and concealment of treatment allocation was determined in only three of the studies after contact with the study author (all three studies were by the same author). Perhaps, if all study authors had been successfully contacted, this would have been clarified for all of the studies.

None of the studies followed the CONSORT reporting guidelines [86]. Consequently, there were no reports on numbers of patients excluded from the studies prior to randomization and there was no information on how those included differed from those who were excluded. We do not know how this would influence the estimate of effect; however, since the effect in the acute pain subgroup is very robust (note the narrow confidence intervals), we are reasonably confident of the results.

Although all studies reported data on side effects and withdrawals, none reported on compliance with the chosen treatment. Compliance can be a confounding factor when studying the effectiveness of any treatment; when the compliance is generally low (usually a matter of self-selection), it is difficult to be certain of the real effectiveness of the treatment.

Potential biases in the review process

The two review authors who assessed the methodological quality were not blinded for authors, journal, or institution. The potential bias caused by the non-blinded quality assessment was expected to be low as neither review author had a conflict of interest. Specifically, the review authors did not have any (financial or other) interest in positive or negative results. Furthermore, we searched the gray literature extensively for eligible trials, presented the search strategy and the inclusion criteria list, and all of the final results of the assessment so that readers can make their own determinations of the results and our conclusions.

There is a possibility of publication bias or study selection bias in this meta-analysis. For example, by missing unpub-

lished negative trials, we may be overestimating the treatment effect of calcitonin. However, a comprehensive search of the published literature for potentially relevant studies was conducted using a systematic strategy to avoid bias. This was followed by attempts to contact corresponding and first authors as we recognize that unpublished or negative trials may exist. We did identify three relevant trials that were not included in the meta-analysis; however, despite concerted efforts to communicate with the authors to clarify methodological issues and obtain additional data, we were unable to locate primary study authors and therefore could not include them in the analysis.

Authors' conclusions

Implications for practice

OVCFs are a significant problem for which many older adults seek medical attention, some of whom are subsequently admitted to hospital. The evidence from this meta-analysis suggests that calcitonin should be considered as an adjunctive analgesic for acute pain associated with recent OVCF. When comparing the route of calcitonin administration, injections may provide more rapid analgesic effect, reducing the time to return to mobilization; however, this observation requires confirmation. Despite a small statistically significant improvement in pain scores at 6 months, there is insufficient evidence to support the use of calcitonin for chronic back pain attributed to remote OVCFs.

Implications for research

Further RCTs, with adequate sample sizes, are necessary to elucidate the analgesic properties of calcitonin and the significance of side effects. Future research should focus on effective dose ranges and their duration of response and the long-term efficacy of calcitonin, particularly in post-menopausal women in whom the majority of OVCF fractures are seen. A cost analysis of calcitonin therapy vs. conventional therapy (e.g., narcotics, newer COX-2-inhibitors, etc.) taking into account health-related quality of life issues, length of time to mobilization, length of hospital stay, and patient preference all need careful consideration when choosing one treatment over another. Finally, trials comparing calcitonin to other analgesics or in combination with other analgesics are needed. Considering the complexity of pain control, it may not be reasonable to look for a single drug to control the severe pain of vertebral compression fractures.

Conflicts of interest None.

Appendix 1 MEDLINE search strategy

1. control group/
2. meta analysis/
3. random$.mp.
4. ((singl$ or doubl$ or tripl$ or trebl$) adj10 (blind$ or mask$)).mp.
5. (cross?over or placebo$ or control$ or factorial or sham$).mp.
6. (meta?analy$ or systematic review$).mp.
7. (therapy or treat$).mp.
8. ((clin$ or intervention$ or compar$ or experiment$ or preventive or therap$) adj10 (trial$ or study or studies)).mp.
9. exp Experimentation/or clinical research.mp. or exp Treatment Effectiveness Evaluation/
10. (longitudinal study or meta analysis or program evaluation or prospective study or retrospective study or treatment outcome study or empirical study or experimental replication or followup study).fc.
11. ((prospective or retrospective or longitudinal or followup or evaluation or outcome$) adj10 (trial$ or study or studies)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
12. (follow adj2 study).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
13. (follow adj2 studies).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
14. or/1–13
15. exp clinical trial/
16. randomi?ed.ti,ab.
17. placebo.ti,ab.
18. dt.fs.
19. randomly.ti,ab.
20. trial.ti,ab.
21. groups.ti,ab.
22. or/15–21
23. animal/
24. human/
25. 23 not (23 and 24)
26. 22 not 25
27. exp osteoporosis/
28. exp bone demineralization, pathologic/
29. osteoporosis.tw.
30. or/27–29
31. calcitonin/
32. calcitonin.tw.
33. calcitonin.rn.
34. or/31–33
35. 30 and 34
36. fracture.tw.
37. 35 and 36
38. 37 and 26

39. 37 and 14
40. 38 and 39

Appendix 2

Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/ exclusions where reported, and any re-inclusions in analyses performed by the review authors	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/ entries were prespecified in the review's protocol, responses should be provided for each question/entry	Was the study apparently free of other problems that could put it at a high risk of bias?

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