BMJ Open

Parathyroid hormone analogues for fracture healing: protocol for a systematic review and meta-analysis of randomised controlled trials

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To cite: Lou S, Lv H, Li Z, *et al*. Parathyroid hormone analogues for fracture healing: protocol for a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2018;**8**:e019291. doi:10.1136/bmjopen-2017-019291

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-019291).

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Received 23 August 2017
Revised 21 November 2017
Accepted 7 December 2017

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ABSTRACT

Introduction Fracture healing is a complex physiological process. Impaired healing will increase the need for care and cause serious complications. Thus, identifying strategies to accelerate the rate of healing, preventing delayed unions and non-unions, is essential. Parathyroid hormone (PTH) is a key systemic regulator of calcium and phosphate metabolism. It has been determined that intermittent administration of PTH and its analogue can exert anabolic effect on bone, increase bone mass and reduce bone loss, leading to an increase in bone formation. Owing to their anabolic effect, there is an increasing interest in its potential in promoting the process of fracture healing. However, in clinical studies, the results are in conflict. This objective of this study is to determine the role of PTH analogues for fracture healing in adults.

Methods and analysis MEDLINE, EMBASE and Cochrane databases will be searched to identify all randomised controlled trials (RCTs) and quasi-RCTs that compare the different effects between PTH analogues and any other treatments in adults with any type of fracture. The primary outcome is the functional recovery. And the secondary outcomes are fracture union and adverse events. The meta-analysis will be performed using a random effects model. Heterogeneity will be assessed by the P values and I^2 statistic. And subgroup analyses and sensitivity analyses will be used to explore the heterogeneity. Risk of bias will be assessed using the Cochrane tool and the quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Ethics and dissemination Ethical approval is not required because this proposed systematic review and meta-analysis is based on published data, without including confidential personal data or data on interventions on patients. The findings of this study will be published in a peer-reviewed journaland presented at a relevant conference.

PROSPERO registration number CRD42017062093.

Strengths and limitations of this study

- A wide search strategy.
- Use of subgroup analyses and sensitivity analyses to explore the heterogeneity.
- Using the Grading of Recommendations Assessment, Development and Evaluation approach to evaluate the certainty of evidences.
- Results may yield significant heterogeneity that cannot be explained.
- Make informed decision about parathyroid hormone and teriparatide of fracture healing.

INTRODUCTION

Rationale

Fracture healing is a complex physiological process[1]; the purpose of which is to restore the continuity and function of the damaged bone.[2] Impaired healing delays the rehabilitation process and leads to delayed union, non-union and defect, which will increase the need for care and cause serious complications. It will deeply affect the quality of life for the patients. Meanwhile, the related costs will cause a heavy economic burden to the society and family. Thus, identifying strategies to prevent delayed unions and non-unions in individuals with impaired bone healing, as well as accelerate the rate of healing in healthy individuals, is essential.[3]

Parathyroid hormone (PTH) is a key systemic regulator of calcium and phosphate metabolism.[4] To date, there are several kinds of PTH analogues, such as PTH 1-84, teriparatide and abaloparatide. PTH 1-84 is a full-length recombinant human PTH. Teriparatide is a synthetic polypeptide hormone consisting of the 1-34 fragment of PTH, which retains most of the biological activities of PTH.[5 6] Abaloparatide is a synthetic peptide analogue of human PTH-related protein. All these three drugs are approved for the treatment of osteoporosis.[7–9] It has been determined that intermittent administration of PTH analogues exerts anabolic effect on bone, increases bone mass and reduces bone loss, leading to an increase in bone formation.[10–16]

Owing to their anabolic effect, there is an increasing interest in its potential in promoting the process of bone healing. In animal experiments, several studies have demonstrated that PTH analogues can produce an anabolic effect during the whole remodelling stage of bone healing.[17–21] However, in clinical studies, the results are in conflict. Some studies indicate that daily intermittent systemic administration of PTH analogues provides a beneficial effect on fracture healing.[22–28] But some trials show that PTH analogues have no effect to increase fracture healing or decrease pain.[29–32] Since evidence-based evaluation of this issue is limited, the effect of PTH analogues on bone healing remains controversial.[33] Thus, an absence of a high-quality evidence provides the impetus for this systematic review and meta-analysis.

Objective

The primary objective of this study is to determine the role of PTH analogues for fracture healing in adults. We aim to conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) to compare the different effects between PTH analogues and any other treatments (eg, anti-osteoporosis drugs, placebo, etc), with functional recovery, fracture union and adverse events as outcomes.

METHODS

This systematic review and meta-analysis protocol has been registered with the International Prospective Register of Systematic Reviews (CRD42017062093). This protocol is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidance.[34]

Eligibility criteria

Participants

This systematic review and meta-analysis will include studies involving adult patients (age >16 years) with fracture regardless of type (fracture, delayed union, non-union or stress fracture), location (long bone, short bone, flat bone or irregular bone) or treatment (operative or conservative).

Interventions

The interventions are teriparatide, PTH 1-84, abaloparatide or other PTH analogues with any route, dose or frequency. We also will include trials where PTH analogues are used as an adjunctive therapy to operative or conservative treatments.

Comparators

The comparators are any other anti-osteoporosis drugs (eg, raloxifene, denosumab, alendronate, etc), placebo or no additional treatment.

Outcomes

The outcomes will include (1) functional recovery, (2) fracture union and (3) adverse events.

Study characteristics

Only the following study designs will be included: RCTs and quasi-RCTs. Quasi-RCTs are trials that use the quasirandom method (eg, allocation by date of birth, day of the week, medical record number or month of the year, etc) of allocating participants to different interventions. Trials published as abstracts, review articles, editorials and letters will be not included.

Information sources

The following three databases will be systematically searched from 1 January 1980 to 1 January 2018, with no language restrictions: (1) MEDLINE, (2) EMBASE and (3) Cochrane Central Register of Controlled Clinical Trials (CENTRAL). In addition, a manual search of all the bibliographies of the retrieved articles and relative reviews will be conducted to further identify potentially eligible trials. Moreover, ClinicalTrials.gov (http://www.clinicaltrials.gov) will be searched to identify studies of interest not yet published.

Search strategy

Search strategies will be developed using medical subject headings as well as text words associated with terms relevant to 'teriparatide', 'parathyroid hormone', 'abaloparatide', 'parathyroid hormone related protein' together with 'randomized controlled trial'. Preliminary search strategies used in MEDLINE, EMBASE and CENTRAL are provided in online supplementary file 1. The searches will be conducted by two authors independently (SL, HL).

Study records

Data management

Literature search results are managed through EndNote X7, which will be used to remove duplicate records. All extracted data are stored in a Microsoft Excel spreadsheet.

Selection process

The process of study selection will be shown in a PRISMA-compliant flow chart (figure 1), all carried out by two authors (SL, HL), with a third author (ZL) available to help resolve any disagreement. As a first step, SL and HL will independently review titles and abstracts of all retrieved articles and exclude the studies that obviously do not fulfil the eligibility criteria. And then, each author will further review the full texts of the remaining studies to determine whether they meet the eligibility criteria. If multiple reports are found in the same study, the results of that study will be collated together.

Data collection process

Two authors (SL, HL) will carefully and independently extract data from all eligible publications in duplicate. Disagreements will be resolved through discussion, or through the help of a third author (YW) if necessary. For missing data, we will seek supplementary appendices and contact study authors via email to obtain the original data. We will allow a delay of 12 weeks to receive a response following two reminder emails at 4 and 8 weeks.

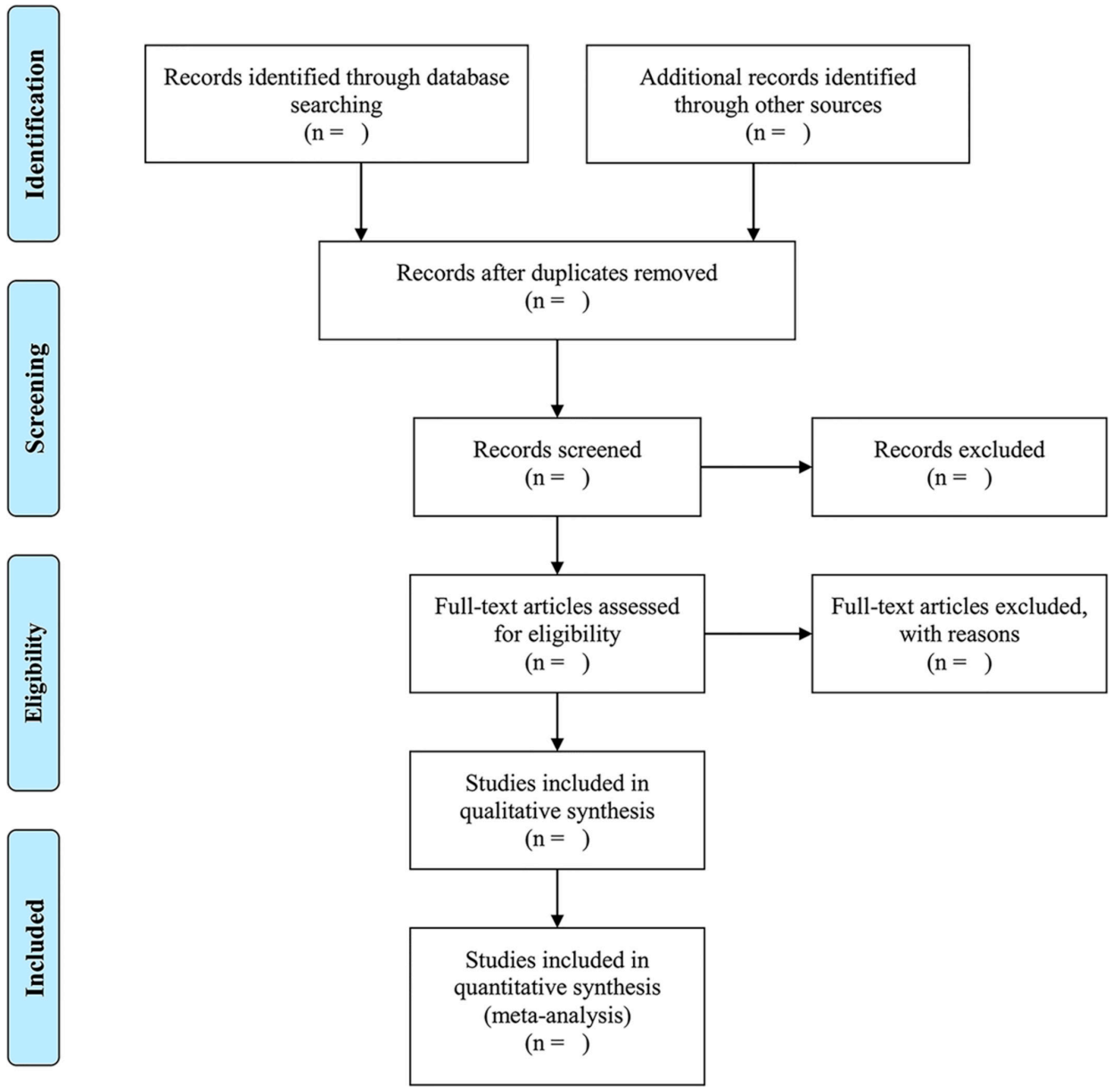

Figure 1 The primary selection process.

Data items

The following data will be extracted: (1) study characteristics (eg, author, journal, year, blinding, randomisation, group design, etc); (2) participant characteristics (eg, age, sex, ethnicity, height, body weight, etc); (3) intervention details (eg, intervention, comparator, cointervention, dosage, frequency, route, duration, etc); (4) outcome measures (eg, sample sizes, means and SDs, adverse events, etc).

Outcomes and prioritisation

Since patients considered functional recovery as a critical outcome, while expressing little interest in the commonly reported surrogate outcome of fracture union,[35] the primary outcome in this study will be functional recovery. Functional recovery is defined as an improvement in mobility, and will be assessed by scales and tests, such as Timed 'Up and Go' test, the self-administered 'Patient-Rated Wrist Evaluation' questionnaire, 'Disabilities of the Arm, Shoulder and Hand' score and the 'Johanson Hip Rating Questionnaire'. The secondary outcomes will include fracture union and adverse events. Fracture union, as determined by radiography, which is defined as a callus is presently bridging at least three of four cortices on orthogonal radiographs.[36] Adverse events will include nausea, sweating, hypercalcaemia, headache, dizziness, depression and other adverse events related to PTH analogues.

Risk of bias in individual studies

Two reviewers (SL, HL) will independently assess risk of bias for each included study. Any disagreement will be resolved through discussion or will be judged by a third reviewer (PT). The tool developed by the Cochrane

Collaboration will be used to assess the risk of bias in the following seven categories: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); (7) other bias.[37] Each item will be classified as having either a high, low or unclear risk of bias, and reasons for each assessment will be documented.

Data synthesis

For dichotomous outcomes, such as adverse events, a risk ratio with 95% CI will be reported. For continuous outcomes, such as difference in mean function score, a standardised mean difference will be used to express the result.

Meta-analysis is performed by a random effects model, which provides more conservative estimated effects.[38] Statistical heterogeneity of results from individual studies will be explored using the P values (P<0.10 indicates significant heterogeneity) and I^2 statistic (I^2>50% indicates significant heterogeneity).[39]

If substantial heterogeneity (I^2>50%) is present and the number of included studies is sufficient, subgroup analyses will be used to identify reasons for heterogeneity, based on the following variables: (1) upper limb, lower limb or axial skeleton; (2) short-term treatment (duration <6 moths) or long-term treatment (duration >6 months); (3) low risk or high risk. In addition, sensitivity analyses will be conducted to examine the robustness of our analysis by omitting specific trials from the overall analysis.

If quantitative synthesis is not appropriate, we will just perform a narrative, qualitative summary and the information will be presented using text and tables.

Meta-bias

If 10 or more studies are included in the meta-analysis, small-study effects for primary and secondary outcomes will be qualitatively analysed using funnel plots as well as qualitatively analysed using Egger's tests.[40 41] If available, reporting bias is assessed by comparing the study findings with its protocol.

Confidence in cumulative evidence

The quality of the evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[42] This approach will assess the risk of bias, consistency, directness, imprecision and publication bias. The overall quality of evidence will be rated as high, moderate, low or very low. This process will be performed using the GRADEpro online software (http://gradepro.org).

Contributors PT and YW are the guarantors. SL, HL and ZL contributed to the conception and design of this study protocol. SL registered the protocol with the PROSPERO database and edited the draft protocol. The search strategy was developed by SL and ZL. SL and HL will screen titles, abstracts and full-text copies of the studies after the literature search. SL, HL or ZL will extract information of the included studies after screening. PT and YW will check the data entry for accuracy and completeness. PT and YW will give advice for data analysis and presentation of study result. All the authors drafted and critically reviewed this manuscript and approved the final version.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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