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Norio Yamamoto[1], Takahisa Ogawa[2], Masahiro Banno[3], Jun Watanabe[3], Tomoyuki Noda[4], Haggai Schermann[5], Toshifumi Ozaki[6]

[1]Department of Orthopedic Surgery, Kagawa Prefectural Central Hospital, Kagawa, Japan;
[2]Department of Orthopedic Surgery, Tokyo Medical and Dental University, Tokyo, Japan;
[3]Systematic Review Workshop Peer Support Group (SRWS-PSG), Japan;
[4]Department of Musculoskeletal Traumatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;
[5]Department of orthopedics ,Foot and Ankle Research and Innovation Laboratory, Massachusetts General Hospital, Boston, USA;
[6]Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan

Norio Yamamoto

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Norio Yamamoto MD1,2, Takahisa Ogawa MD, MPH3, Masahiro Banno, MD, PhD2,4,5,
Jun Watanabe MD, PhD2, 6, 7, Tomoyuki Noda, MD, PhD8, Haggai Schermann, MD, MPH9Toshifumi Ozaki, MD, PhD10

1 Department of Orthopedic Surgery, Kagawa Prefectural Central Hospital, Kagawa, Japan
2 Systematic Review Workshop Peer Support Group (SRWS-PSG), Japan
3 Department of Orthopedic Surgery, Tokyo Medical and Dental University, Tokyo, Japan
4 Department of Psychiatry, Seichiryo Hospital, Tsurumai 4-16-27, Showa-ku, Nagoya 466-0064 JAPAN
5 Department of Psychiatry, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya 466-8560 JAPAN
6 Department of Surgery, Tottori Prefectural Central Hospital, 730 Ezu Tottori City, Tottori, 680-0901 Japan
7 Center for Community Medicine, Jichi Medical University, 3311-1 Yakushiji Shimotsuke City, Tochigi, 329-0498 Japan
8 Department of Musculoskeletal Traumatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
9 Department of orthopedics ,Foot and Ankle Research and Innovation Laboratory,
Massachusetts General Hospital, Boston, USA
10 Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan

Corresponding author: Norio YAMAMOTO, MD
Department of Orthopedic Surgery, Kagawa Prefectural Central Hospital, Kagawa, Japan
1-2-1, Asahi-machi, Takamatsu, Kagawa 760-8557, Japan
Tel.: +81 87 811 3333; Fax: +81 87 802 1188
E-mail: norio-yamamoto@umin.ac.jp

1.Introduction

Demographic development has resulted in an increased incidence of geriatric hip fractures [1, 2].Patients with hip fractures becoming older and increasingly frail [2]. More trochanteric fractures than neck fractures among hip fractures occurred [1, 2]. Trochanteric fractures lead to increased mortality and a significant socio-economic burden [3]. To prevent complications of immobilization, rigid fracture fixation should allow early mobilization of the patient with immediate full weight bearing.

There are some complications for internal fixation, such as screw cut out, cut through, which results in reoperation. The mechanical failure is due to instability by breakdown of the interface between femoral head and lag screw, caused by combined axial loads and rotational moments during walking gait [4, 5, 6]. Recent reports suggested that the cement enhances the implant anchorage within the head-neck fragment and leads to good functional results with less complications [7, 8]. However, it still remains unclear whether the cement augmentation could be a better fixation option when compared with conventional internal fixation alone.

The purpose of this study is to determine the efficacy and safety of cement augmentation for internally-fixed trochanteric fractures using a systematic review and meta-analysis.

2.Research question

P: Patient with internal fixation for trochanteric fracture
I: ”Conventional internal fixation" plus "cement augmentation”
C: ”Conventional internal fixation" plus "sham interventions or non-intervention or usual care”
O: Fixation failures, Parker Mobility Score, 1-year mortality rate, EQ-5D (Functional outcomes: patient-reported measures of hip function), and adverse events

3.Method

3.1 Inclusion criteria of the articles for the review

3.1.1 Type of studies

We will include randomised controlled trials that assess cement augmentation on internal fixation for trochanteric fracture. We will not apply language or country restrictions. We will include all papers including published, unpublished articles, abstract of conference and letter.
We will exclude crossover trials,quasi-experimental studies and quasi-randomized trials. We will not exclude studies based on the observation period.

3.1.2 Study participants

Patients who has sustained trochanteric fracture and undergoes internal fixation as operative treatment

Inclusion criteria:

Fracture type: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopedic Trauma Association (AO/OTA) classification 31A [9].
The ability to walk with or without supportbefore the fracture.

Exclusion criteria:

Pathological fractures, open fractures, history of allergy to cement

3.1.3 Intervention

“Conventional internal fixation" plus "cement augmentation”
Cement will be inserted into or around the screw.
Type of cement: For example, calcium phosphate degradable cement, polymethyl methacrylate (PMMA) cement. We do not set type of cement restrictions.

3.1.4 Control

"Conventional internal fixation" plus "sham interventions or non-intervention or usual care"

3.2 Type of outcomes

3.2.1 **Primary outcomes**

1. Reoperation
Definition: Indication of reoperations are set by original authors

Incidence proportion of reoperation
Period: during follow up period

2. Ability of mobility
Definition: Parker Mobility Score [10]
Period: between 3 and 12 months follow up (at the longest follow up from 3 months follow up)

3.2.2 Secondary outcomes
1. 1-year mortality rate
Definition: incidence proportion of death during 1-year follow up period
Period: during 1-year follow up period

2. Functional outcomes: patient-reported measures of hip function
Definition: EuroQoL 5 dimensions (EQ-5D) 3-level (3L) [11] or 5-level (5L) [12, 13]
Period: between 3 and 12 months follow up (at the longest follow up from 3 months follow up)

3. All adverse events
Definition: definition of adverse events are set by original authors.
Incidence proportion of all adverse events
Period: during follow up period

4. Fixation failures
Definition: Screw cut-out, penetration of the implant into the hip joint, loosening, implant breakage, non-union, and prominent screw by over sliding distance, for which reoperation is indicated or performed.
The definition of the fixation failure will be set by the authors of the original study.
Incidence proportion of all fixation failures
Period: during follow up period

3.3 Search method
3.3.1 Electronic search
We will search the following databases:
1. the Cochrane Central Register of Controlled Trials(CENTRAL) ;
2. MEDLINE via Pubmed
3. EMBASE via PROQUEST
See Appendix 1, 2, and 3 for the search strategies.

3.3.2 Other resources
We will also search the following databases for ongoing or recently completed trials:
1. the World Health Organization International Clinical Trials Platform Search Portal (ICTRP)
2. ClinicalTrials.gov.
See Appendix 4, 5 for the search strategies.
We will check the reference lists of studies, including international guidelines [14, 15] as well as the reference lists of eligible studies and articles citing eligible studies. We will ask the authors of original studies for unpublished or

additional data.

3.4 Data extraction

3.4.1 Selection of the studies

Two independent reviewers (NY,TO, and HS) will screen every title and abstract of the articles. Articles extracted by reviewers will be included in the full text review. Each reviewer will independently perform study selection. We will make contact with original authors if there is any disagreement regarding the articles. The two reviewers will compare their lists and any differences in opinion will be resolved by discussion or, if necessary by consulting the third reviewer (JW).

3.4.2 Data extraction and management

Two reviewers (NY and TO) will perform independent data extraction of the included trials using data collection form, which is pre-checked by ten randomly selected studies. The data collected will include information on study design, study population, interventions and outcomes, and results. Any disagreements regarding the data extraction will be resolved by discussion or, if necessary by consulting a third reviewer (JW).

3.5 Risk of bias

Two reviewers (NY and TO) will assess risk of bias independently. We will use the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) tool. Any disagreements regarding the risk of bias will be resolved by discussion or, if necessary by consulting a third reviewer (JW).

3.6 Assessment of the treatment effect

We will perform meta-analysis and calculate relative risk and 95% confidence intervals (CIs) about the following bivariate variables: fixation failures, 1-year mortality rate.
We will perform meta-analysis and calculate mean difference (MD) and 95% CI about the following continuous variables: Parker Mobility Score, EQ-5D.
We will summarize adverse events based on the definition by the original article, but we will not perform meta-analysis..

3.7 Method of synthesis

We will analyse the mean and standard deviation of continuous data based on the method by Cochrane handbook [16]. For the functional outcome such as Parker Mobility Score or EQ-5D, we will define the functional outcome as the score assessed at the longer follow up period after the intervention. We will include the cluster-randomised trials that report an estimate of the intracluster (or intraclass) correlation coefficient (ICC) in meta-analysis.

3.8Handling of missing data

3.8.1 Missing participants

For dichotomous data

We will perform the intention-to-treat (ITT) analysis for all dichotomous data as much as possible. We will also include missing participants for analysis.
For those dropped out from the study early, they are assumed to have the same rates of negative outcome on the basis of the rates of those who completed the study.

For continuous data
We will not impute missing data based on the recommendation by Cochrane handbook [16]. We will perform meta-analysis about the available data in the original study.

3.8.2Missing values
We will ask missing values to the original authors.

3.8.3Missing statistics
When original studies only report standard error or p-value, we will calculate the standard deviation based on the method by Altman [17]. If we don't know these values when we contact the authors, standard deviation will be calculated by confidence interval and t-value based on the method by Cochrane handbook [16], or validated method [18]. Validity of these methods will be analysed by sensitivity analysis.

3.9 Assessment of heterogeneity
We will evaluate the statistical heterogeneity by visual inspection of the forest plots and calculating the I^2 statistic (I^2 values of 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). When there is substantial heterogeneity (I^2> 50%), we will assess the reason of the heterogeneity. Cochrane Chi^2test (Q-test) will be performed for I^2 statistic, and P value less than 0.10 will be defined as statistically significant.

3.10 Assessment of reporting bias
We will search the clinical trial registry system (ClinicalTrials.gov and ICTRP) and will perform extensive literature search for unpublished trials. We will assess the potential publication bias by visual inspection of the funnel plot. Egger test will be performed as well. We will not conduct the test when we find less than 10 trials or trials which have similar sample size.We will assess the potential publication bias by visual inspection of the funnel plot

3.11 Meta-analysis
Meta-analysis will be performed using Review Manager software (RevMan 5.4). We will use a random-effects model.

3.12 Subgroup analysis
To elucidate the influence of effect modifiers on results, we will evaluate the subgroup analyses of the primary outcomes on the following factors when sufficient data are available.
1. (For participants) Type of fracture: subgroups will be AO/OTA classification 31A1, A2, A3
2. (For participants) Type of implant used for internal fixation: subgroups will be intramedullary nailing and extramedullary implant (such as sliding hip screw).
3. (For intervention)Type of cement augmentation: subgroups will be calcium phosphate degradable cement, PMMA cement, and similar substances.

3.13 Sensitivity analysis
We will undertake sensitivity analyses for the primary outcome to assess whether the results of the review are robust to the decisions made during the review process. We plan to examine the effects of the review findings of:

1. Exclusion of studies using imputed statistics.
2. Missing participants: verify the robustness of the results by seeking informative missingness odds ratios.
3. Only the participants who complete the study with complete data
4.. Measurement-period adjustment: The functional outcome, such as Parker Mobility Score, EQ-5D, assessed at 1 year follow up

4. Summary of findings table

Summary of findings table will be made for the following outcome based on the Cochrane handbook [16].
We will include grading to evaluate the quality of evidence based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for each Summary of findings table [16, 19].
1. Fixation failures
2. Parker Mobility Score
3. 1-year mortality rate
4. EQ-5D
5. All adverse events

5. Conflict of Interest

The authors declare no conflicts of interests.

Appendix 1: CENTRAL search strategy
([mh “Hip Fractures”] OR [mh “Fracture Fixation, Internal”] OR intertrochanteric fracture*:ti,ab OR trochanteric fracture*:ti,ab OR pertrochanteric fracture*:ti,ab OR nail:ti,ab OR sliding hip screw*:ti,ab) AND ([mh “Bone Cements”] OR [mh Cementoplasty] OR [mh “polymethyl methacrylate”] OR [mh “calcium phosphates”] OR cement*:ti,ab OR polymethyl methacrylate:ti,ab OR calcium phosphates:ti,ab OR CaP∗:ti,ab)

Appendix 2: MEDLINE (via PubMed)search strategy
#1 “Hip Fractures” [mh]
#2 “Fracture Fixation, Internal” [mh]
#3 intertrochanteric fracture* [tiab]
#4 intertrochanteric femoral fracture* [tiab]
#5 trochanteric fracture* [tiab]
#6 pertrochanteric fracture* [tiab]
#7 nail* [tiab]
#8 sliding hip screw* [tiab]
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 “Bone Cements” [mh]
#11 Cementoplasty [mh]
#12 “polymethyl methacrylate” [mh]
#13 “calcium phosphates” [mh]
#14 cement* [tiab]
#15 polymethyl methacrylate [tiab]
#16 “calcium phosphates” [tiab]
#17 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16

#18 “drug therapy”[sh]
#19 randomly[tiab]
#20 trial[tiab]
#21 groups[tiab]
#22 randomized[tiab]
#23 placebo[tiab]
#24 “randomized controlled trial”[pt]
#25 “controlled clinical trial”[pt]
#26 animals [mh]
#27 humans [mh]
#28 #18 OR #19 OR #20 OR #21 OR #24 OR #25 OR #26 OR #27 NOT (#26 NOT #27)
#29 #9 AND #17 AND #28

Appendix 3: EMBASE search strategy
S1 (EMB.EXACT.EXPLODE("hip fracture"))
S2 EMB.EXACT.EXPLODE("osteosynthesis")
S3 (ab(intertrochanteric fracture) OR ti(intertrochanteric fracture) OR ab(intertrochanteric fractures) OR ti(intertrochanteric fractures))
S4 (ab(intertrochanteric femoral fracture) OR ti(intertrochanteric femoral fracture) OR ab(intertrochanteric femoral fractures) OR ti(intertrochanteric femoral fractures))
S5 (ab(trochanteric fracture) OR ti(trochanteric fracture) OR ab(trochanteric fractures) OR ti(trochanteric fractures))
S6 (ab(pertrochanteric fracture) OR ti(pertrochanteric fracture) OR ab(pertrochanteric fractures) OR ti(pertrochanteric fractures))
S7 (ab(nail) OR ti(nail) OR ab(nails) OR ti(nails))
S8 (ab(sliding hip screw) OR ti(sliding hip screw) OR ab(sliding hip screws) OR ti(sliding hip screws))
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (EMB.EXACT.EXPLODE("bone cement"))
S11 EMB.EXACT.EXPLODE("cementoplasty")
S12 (EMB.EXACT.EXPLODE("poly(methyl methacrylate)"))
S13 (EMB.EXACT.EXPLODE("calcium phosphate"))
S14 (ab(cement) OR ti(cement) OR ab(cements) OR ti(cements))
S15 (ab(polymethyl methacrylate) OR ti(polymethyl methacrylate) OR ab(polymethyl methacrylates) OR ti(polymethyl methacrylates))
S16 (ab(calcium phosphates) OR ti(calcium phosphates))
S17 (ab(CaP) OR ti(CaP))
S18 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S19 S9 AND S18
S20 (ab(random*) OR ti(random*)) OR (ab(placebo*) OR ti(placebo*)) OR (ab(double NEAR/1 blind*) OR ti(double NEAR/1 blind*))
S21 S19 AND S20

Appendix 4: ICTRP search strategy

(“Hip Fractures” OR “Fracture Fixation” OR “intertrochanteric fracture”
OR “trochanteric fracture” OR “pertrochanteric fracture” OR “nail” OR “sliding hip screw”)
AND
(“Bone Cements” OR “Cementoplasty” OR “polymethyl methacrylate” OR “calcium phosphates” OR “cement” OR “polymethyl methacrylate” OR “calcium phosphates” OR “CaP”)

Appendix 5: ClinicalTrials.gov search strategy
Condition or disease: Hip Fracture OR Fracture Fixation OR intertrochanteric fracture
OR trochanteric fracture OR pertrochanteric fracture OR nail OR sliding hip screw
Intervention: Cement OR Cementoplasty OR polymethyl methacrylate OR calcium phosphates OR CaP

Appendix 7
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