Bone & Joint Open

# Supplementary Material

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## Supplementary Methods 1

### Calculating standard mean difference and standard error from odds ratio and confidence interval data

If necessary, standard mean differences (SMD) and corresponding standard error (SE) of discontinuous outcome data were calculated from the odds ratio (OR) and 95% confidence interval (CI), respectively, using Chinn's method.[1] This approach is summarized by Equations 1 and 2 and recommended by the contemporaneous Cochrane Handbook for Systematic Reviews of Interventons:[1,2]

$$\mathrm{SMD} = \frac{\sqrt{3}}{\pi}\ln(\mathrm{OR}) \quad (1)$$

$$\mathrm{SE} = \frac{\sqrt{3}}{\pi}\ln(95\%\mathrm{CI}) \quad (2)$$

## Supplementary Methods 2

### Adaptive method for imputing standard deviation from range and sample size

Where necessary, standard deviation (SD) was imputed from sample range value using Wan et al's[3] adaptive method, outlined in Equations 3 to 7.

$$\mathrm{S} \cong \frac{\mathrm{b}-\mathrm{a}}{\xi(\mathrm{n})} \quad (3)$$

$$\xi(\mathrm{n}) = 2.\mathrm{E}(\mathrm{Z}_{(n)}) \quad (4)$$

$$\mathrm{E}(\mathrm{Z}_{(n)}) = \mathrm{n}\int_{-\infty}^{\infty} \mathrm{z}[\Phi(\mathrm{z})]^{n-1}\,\phi(\mathrm{z})\mathrm{dz} \quad (5)$$

$$\phi(\mathrm{z}) = \frac{1}{\sqrt{2\pi}}\mathrm{e}^{\frac{-z^2}{2}} \quad (6)$$

$$\Phi(\mathrm{z}) = \int_{-\infty}^{z} \phi(\mathrm{t})\mathrm{dt} \quad (7)$$

In the above equations, *S* describes sample SD; *a* and *b* are the minimum and maximum values, respectively. $E(Z_n)$ is the expected value of $Z_n$, and is calculated as anticipated by David and Nagaraja.[3,4] Equation 6 describes the probability density function of the sample; while Equation 7 represents the cumulative distribution of the standard normal distribution.[3,4]

## Supplementary Results 1

### Additional information on excluded studies

Two possibly eligible studies were excluded during our study selection process. Firstly, the 2005 abstract presented by Larsson et al[5] presented the results of a randomized controlled trial (RCT) of complex (Type 41-B2 or Type 41-B3, OTA classification) tibial plateau fractures, treated with open reduction and internal fixation. Patients were randomized to either calcium phosphate cement (synthetic) or anterior iliac autologous bone grafting.[5] Radiostereometry to assess translation of the articular fragment over a one-year follow-up period and this was correlated with functionality, assessed using the Lysholm Knee Score.[5] The authors concluded that calcium phosphate cement provided a more stable fixation of the elevated fragment than autologous bone graft. Unfortunately, we could not assimilate this study as available data were insufficient.[5]

The second study we excluded was a RCT from Dickson et al.[6] This study also compared calcium phosphate cement and iliac bone grafting, with a variety of radiological adverse events and functional outcomes.[6] However, this study's population included patients with tibial (n = 17), calcaneal (n = 15), radial (n = 6), humeral (n = 1), and femoral (n = 1) metaphyseal fractures.[6] As subgroup data for the tibial metaphyseal fractures were unavailable, we excluded this study from our analysis. The authors concluded that calcium phosphate cement was a safe and effective void filler.[6]

**Supplementary Table i.** Search strategy executed on the "MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations 1946 to July 28th, 2021", "EMBASE 1980 to 2021 Week 30", and "Cochrane Central Register of Controlled Trials" databases.

| Row | Search term |
|---|---|
| 1 | Clinical Trial.pt |
| 2 | Controlled Clinical Trial.pt |
| 3 | Randomized Controlled Trial.pt |
| 4 | Pragmatic Clinical Trial.pt |
| 5 | RCT.pt |
| 6 | Randomized Controlled Trial/ |
| 7 | Clinical Trial/ |
| 8 | Controlled Clinical Trial/ |
| 9 | Pragmatic Clinical Trial/ |
| 10 | Randomized Clinical Trial |
| 11 | Intervention.tw |
| 12 | OR/1-11 |
| 13 | Tibia/ |
| 14 | Tibi*.tw |
| 15 | Knee/ |
| 16 | Knee Joint/ |
| 17 | OR/13-16 |
| 18 | Tibia Fracture/ |
| 19 | ((Plateau or Articular or Intra?articular or Proximal) and Fracture$1).tw. |
| 20 | Knee Injuries/ |
| 21 | OR/18-20 |
| 22 | AND/12,17,21 |
| 23 | Transplantation, Autologous/ |
| 24 | Bone Transplantation/ |

| | |
|---|---|
| 25 | (Bone AND (Autologous OR Graft)).tw |
| 26 | Bone Substitute/ |
| 27 | ((Tricalcium and Phosphate) or beta-TCP or B-TCP or alpha-TCP or A-TCP).tw. |
| 28 | (Bone Substitute).tw. |
| 29 | OR/23-28 |
| 30 | 22 AND 29 |
| 31 | Deduplicate 30 |

**Supplementary Table ii.** RoB2 Risk of bias evaluation for included studies.

| Study name | Risk of bias arising from the randomization process | Risk of bias due to deviations from the intended intervention | Risk of bias due to missing outcome data | Risk of bias in measurement of the outcome | | | | | | | | Risk of bias in selection of reported result | | | | | | | | Overall risk of bias | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | A | B | C | D | E | F | G | H | A | B | C | D | E | F | G | H | A | B | C | D | E | F | G | H |
| Buchholz et al (1989)[7] | - | ↓ | ↓ | - | X | X | ↓ | ↓ | ↑ | X | X | ↓ | X | X | ↓ | ↓ | ↓ | X | X | - | X | X | - | - | ↑ | X | X |
| Russell et al (2008)[8] | ↓ | ↓ | ↓ | X | ↓ | ↓ | ↓ | ↓ | X | X | X | X | ↓ | ↓ | ↓ | ↓ | X | X | X | X | ↓ | ↓ | ↓ | ↓ | X | X | X |
| Heikkilä et al (2010)[9] | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | X | X | X | ↓ | X | ↓ | ↓ | ↓ | X | X | X | ↓ | X | ↓ | ↓ | ↓ | X | X | X | ↓ | X |
| Pernaa et al (2011)[10] | ↓ | ↓ | ↑ | ↓ | ↓ | ↓ | ↓ | X | ↓ | X | X | ↓ | ↓ | ↓ | ↓ | X | ↓ | X | X | ↑ | ↑ | ↑ | ↑ | X | ↑ | X | X |
| Jónsson and Mjöberg (2015)[11] | ↓ | ↓ | ↓ | ↓ | ↓ | X | ↓ | ↓ | - | X | ↓ | ↓ | ↓ | X | ↓ | ↓ | ↓ | X | ↓ | ↓ | ↓ | X | ↓ | ↓ | - | X | ↓ |
| Hofmann et al (2019)[12] | ↓ | ↓ | ↓ | X | ↓ | ↓ | ↓ | X | X | ↓ | ↓ | X | ↓ | ↓ | ↓ | X | X | ↓ | ↓ | X | ↓ | ↓ | ↓ | X | X | ↓ | ↓ |

Studies and outcomes with a "High" overall risk of bias were excluded from our meta-analysis.

A: Postoperative Articular Depression; B: Articular Depression at Long-Term Follow-Up; C: Mechanical Alignment at Long-Term Follow-Up; D: Frequency of Surgical Site Infection at Tibial Defect Site; E: Frequency of Secondary Surgical Interventions; F: Defect Site Pain at Long-Term Follow-Up; G: Perioperative Blood Loss; H: Duration of Surgery.

↑ (*Red*): High risk of bias; – (*Yellow*): Some concerns of risk of bias; ↓ (*Green*): Low risk of bias; X: Study lacks data that corresponds to this outcome.

**Supplementary Table iii.** GRADE quality of evidence evaluation for each synthesized outcome.

| Outcome | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty |
|---|---|---|---|---|---|---|
| Postoperative articular reduction | Not serious | Not serious | Not serious | Not serious | N/A | High |
| Long-term articular reduction | Not serious | Not serious[B] | Not serious | Not serious | N/A | High |
| Mechanical alignment at long-term follow-up | Not serious | Not serious | Not serious | Not serious | N/A | High |
| Frequency of surgical site infection at tibial defect site | Not serious | Not serious | Not serious | Serious[C] | N/A | Moderate |
| Frequency of secondary surgical interventions | Not serious | Not serious | Not serious | Serious[C] | N/A | Moderate |
| Defect site pain at long-term follow-up | Serious[A] | Not serious | Not serious | Serious[C] | N/A | Moderate |
| Perioperative blood loss | Not serious | Not serious | Not serious | Not serious | N/A | High |
| Duration of surgery | Not serious | Not serious[B] | Not serious | Not serious | N/A | High |

Given each outcome is constituted of randomised controlled trials, each started at "High" overall certainty (*Green*) and could be downgraded to "Moderate" (*Yellow*), "Serious" (*Orange*) or "Very Serious" (*Red*) according to the most limited constituent domain: not serious (-0, *Green*), serious (-1, *Yellow*) or very serious (-2, *Red*).[13] There were no grounds to upgrade evidence quality.

N/A: Publication bias was not considered due to the limited number of studies included in this meta-analysis.

A: Risk of bias was considered "Serious" if more than one third of constitutive studies had serious or some concerns of risk of bias (Supplementary Table ii). B: Heterogeneity in these outcomes could be explained. C: These outcomes had relatively broad 95% confidence intervals in spanning positive and negative magnitudes. Given the appreciable harm to patients these outcomes represent, it was deemed appropriate to downgrade these outcomes.

**Supplementary Table iv.** List of unanticipated complications requiring secondary surgical intervention in their respective studies.

| Study | Bone substitute | Autologous bone graft |
|---|---|---|
| Bucholz et al (1989)[7] | 1. Premature mobilization resulted in a 15° varus malunion. Resultant prominent hardware facilitated deep wound infection, requiring removal and debridement. Subsequently, the patient developed osteomyelitis, requiring further debridement.<br>2. Contiguous septic knee developed postoperatively, necessitated multiple surgical debridements to resolve. | Two cases of surgical site infection 7 to 12 months postoperatively. These were managed with hardware removal, debridement, and open wound care. |
| Russell et al (2008)[8] | No complications | No complications |
| Jónsson and Mjöberg (2015)[11] | 1. Removal of hardware due to local discomfort (3 years postoperatively) | 1. Developed compartment syndrome postoperatively.<br>2. Removal of hardware due to local discomfort (4 years postoperatively) |

## References


1. **Chinn S.** A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med*. 2000;19(22):3127-3131. doi:10.1002/1097-0258(20001130)19:22<3127::aid-sim784>3.0.co;2-m
2. **Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors).** Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (Updated February 2021). Published online 2021. Accessed 30 September 2021. https://training.cochrane.org/handbook
3. **Wan X, Wang W, Liu J, Tong T.** Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology*. 2014;14(1):135. doi:10.1186/1471-2288-14-135
4. **David HA, Nagaraja HN.** *Order Statistics*. John Wiley & Sons, Ltd; 2003.
5. **Larsson S, Berg P, Sagerfors M.** Augmentation of Tibial Plateau Fractures with Calcium Phosphate Cement: A Randomized Study Using Radiostereometry.

Orthopaedic Trauma Association Annual Meeting 2004. 2004 August; Florida, USA. Accessed September 30, 2021. https://ota.org/sites/files/legacy_abstracts/ota04/otapa/OTA04210.htm

6. **Dickson KF, Friedman J, Buchholz JG, Flandry FD.** The use of BoneSource hydroxyapatite cement for traumatic metaphyseal bone void filling. *J Trauma*. 2002;53(6):1103-1108. doi:10.1097/00005373-200212000-00012
7. **Bucholz RW, Carlton A, Holmes R.** Interporous hydroxyapatite as a bone graft substitute in tibial plateau fractures. *Clin Orthop Relat Res*. 1989;(240):53-62.
8. **Russell TA, Leighton RK, Alpha-BSM Tibial Plateau Fracture Study Group.** Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study. *J Bone Joint Surg Am*. 2008;90-A(10):2057-2061. doi:10.2106/JBJS.G.01191
9. **Heikkilä JT, Kukkonen J, Aho AJ, Moisander S, Kyyrönen T, Mattila K.** Bioactive glass granules: a suitable bone substitute material in the operative treatment of depressed lateral tibial plateau fractures: a prospective, randomized 1 year follow-up study. *J Mater Sci Mater Med*. 2011;22(4):1073-1080. doi:10.1007/s10856-011-4272-0
10. **Pernaa K, Koski I, Mattila K, et al.** Bioactive glass S53P4 and autograft bone in treatment of depressed tibial plateau fractures - a prospective randomized 11-year follow-up. *J Long Term Eff Med Implants*. 2011;21(2):139-148. doi:10.1615/jlongtermeffmedimplants.v21.i2.40
11. **Jónsson BY, Mjöberg B.** Porous titanium granules are better than autograft bone as a bone void filler in lateral tibial plateau fractures: A randomised trial. *Bone Joint J*. 2015;97-B(6):836-841. doi:10.1302/0301-620X.97B6.34552
12. **Hofmann A, Gorbulev S, Guehring T, et al.** Autologous Iliac Bone Graft Compared with Biphasic Hydroxyapatite and Calcium Sulfate Cement for the Treatment of Bone Defects in Tibial Plateau Fractures: A Prospective, Randomized, Open-Label, Multicenter Study. *J Bone Joint Surg Am*. 2020;102-A(3):179-193. doi:10.2106/JBJS.19.00680
13. **Sterne JAC, Savović J, Page MJ, et al.** RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898

14. **Guyatt GH, Oxman AD, Vist GE, et al.** GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD