The Use of Calcium Phosphate Bone Cement in Fracture Treatment. A Meta-Analysis of Randomized Trials

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**Supplementary material**
Commentary and Perspective, data tables, additional images, video clips and/or translated abstracts are available for this article. This information can be accessed at [http://www.ejbjs.org/cgi/content/full/90/6/1186/DC1](http://www.ejbjs.org/cgi/content/full/90/6/1186/DC1)

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The Use of Calcium Phosphate Bone Cement in Fracture Treatment
A Meta-Analysis of Randomized Trials

By Sohail S. Bajammal, MBChB, MSc, FRCSC, Michael Zlowodzki, MD, Amy Lelwica, MD, Paul Tornetta III, MD, Thomas A. Einhorn, MD, Richard Buckley, MD, FRCSC, Ross Leighton, MD, FRCSC, Thomas A. Russell, MD, Sune Larsson, MD, PhD, and Mohit Bhandari, MD, MSc, FRCSC

Investigation performed at the Orthopaedic Research Division, Department of Surgery, McMaster University, Hamilton, Ontario, Canada

Background: Available options to fill fracture voids include autogenous bone, allograft bone, and synthetic bone materials. The objective of this meta-analysis was to determine whether the use of calcium phosphate bone cement improves clinical and radiographic outcomes and reduces fracture complications as compared with conventional treatment (with or without autogenous bone graft) for the treatment of fractures of the appendicular skeleton in adult patients.

Methods: Multiple databases, online registers of randomized controlled trials, and the proceedings of the meetings of major national orthopaedic associations were searched. Published and unpublished randomized controlled trials were included, and data on methodological quality, population, intervention, and outcomes were abstracted in duplicate. Data were pooled across studies, and relative risks for categorical outcomes and weighted mean differences for continuous outcomes, weighted according to study sample size, were calculated. Heterogeneity across studies was determined, and sensitivity analyses were conducted.

Results: We identified eleven published and three unpublished randomized controlled trials. Of the fourteen studies, six involved distal radial fractures, two involved femoral neck fractures, two involved intertrochanteric femoral fractures, two involved tibial plateau fractures, one involved calcaneal fractures, and one involved multiple types of metaphyseal fractures. All of the studies evaluated the use of calcium phosphate cement for the treatment of metaphyseal fractures occurring primarily through trabecular, cancellous bone. Autogenous bone graft was used in the control group in three studies, and no graft material was used in the remaining studies. Patients managed with calcium phosphate had a significantly lower prevalence of loss of fracture reduction in comparison with patients managed with autograft (relative risk reduction, 68%; 95% confidence interval, 29% to 86%) and had less pain at the fracture site in comparison with controls managed with no graft (relative risk reduction, 56%; 95% confidence interval, 14% to 77%). We were unable to compare pain at the bone-graft donor site between the studies because of methodological reasons. Three studies independently demonstrated improved functional outcomes when the use of calcium phosphate was compared with the use of no grafting material.

Conclusions: The use of calcium phosphate bone cement for the treatment of fractures in adult patients is associated with a lower prevalence of pain at the fracture site in comparison with the rate in controls (patients managed with no graft material). Loss of fracture reduction is also decreased in comparison with that in patients managed with autogenous bone graft.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

The incidence of fractures in the United States exceeds 6 million fractures annually. Metaphyseal fractures are among the most difficult fractures to treat. Depressed articular fragments can crush the underlying weak subchondral cancellous bone, leaving a void when the articular segments are reduced surgically. Potential long-term problems

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A commentary is available with the electronic versions of this article, on our web site (www.jbjs.org) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).
such as pain, posttraumatic arthritis, and limitation of motion and function might occur if joint surface subsidence cannot be prevented or at least limited.

Autogenous bone, typically from the iliac crest, remains the preferred source of bone for grafting. However, it is associated with donor-site morbidity, including chronic pain and wound complications\textsuperscript{9-11}. Alternative graft materials for filling fracture voids include allograft bone and synthetic bone materials. While the use of allograft avoids the donor-site morbidity associated with the use of autograft, it also can lead to complications, including potential disease transmission, histoincompatibility, and possibly lower union rates\textsuperscript{9-11}. Therefore, synthetic bone materials, such as different types of calcium phosphate bone cement products, appear to be an attractive alternative because they lack the disadvantage of donor-site morbidity associated with autografts and the disadvantages of potential infection and disease transmission associated with allograft.

Several narrative review articles have addressed the use of bone-grafting for the treatment of fractures and traumatic injuries. Some studies have focused on the use of synthetic bone materials, including different types of calcium phosphate bone cement, and have described the biomechanical, histological, and clinical characteristics of these materials\textsuperscript{9-14}. However, none of the reviews described the search methodology or the criteria for including studies. Thus, it is difficult to assess the comprehensiveness of the reviews and to determine whether bias in selecting studies was avoided. A comprehensive systematic review with explicit transparent reporting of the search methodology and criteria for including studies coupled with a validity assessment of included studies and statistical pooling of studies, when appropriate, allows stronger unbiased inferences to be made.

The objective of the present meta-analysis was to identify and summarize the evidence from randomized controlled trials that compared the use of a type of calcium phosphate bone cement with other alternatives and its effects on functional and radiographic outcomes in adults with fractures of the appendicular skeleton.

We hypothesized that the use of calcium phosphate bone cement improved outcomes in patients with metaphyseal fractures of the upper and lower extremities.

Materials and Methods

Eligibility Criteria

We identified articles in which (1) the target population was skeletally mature patients with a fracture of a bone of the appendicular skeleton, (2) the intervention was the use of calcium phosphate bone cement for the treatment of these fractures (as compared with alternative treatment or no treatment), (3) the outcome was measured on the basis of functional criteria (pain or impairment), radiographic criteria (fracture-healing or subsidence), or the rate of infection, and (4) the study was a published or unpublished randomized controlled trial. We excluded any study that did not meet all of the aforementioned inclusion criteria.

Data Sources and Search Strategy

We conducted, in duplicate (S.S.B. and A.L.) and independently, a computerized search of the electronic databases MEDLINE (from 1966 to September 2006), EMBASE (from 1980 to September 2006), CINAHL (from 1982 to September 2006), and AMED (from 1985 to September 2006). We considered studies in all languages, regardless of publication status. We also searched the Cochrane Database for Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Abstracts of Reviews of Effects, the United Kingdom National Research Register (https://portal.nihr.ac.uk/Pages/NRRArchive.aspx), the ClinicalTrials.gov web site, the Current Controlled Trials (http://controlled-trials.com/mrct/), and archives of abstracts of the annual meetings of the Orthopaedic Trauma Association (www.hwbf.org/ota/am/, 1996-2004), the American Academy of Orthopaedic Surgeons (www.aaos.org/wordhtml/libscip.htm, 2003-2004; accessed September 2006), and the Canadian Orthopaedic Association (www.coa-aco.ca/meeting-archives.html, 2003-2005) to identify additional studies. Additionally, we searched the proceedings of the Eleventh Meeting of the Combined Orthopaedic Associations 2004, Sydney, Australia, by hand. One of us (S.S.B.) reviewed the bibliography of each article that met our inclusion criteria for additional relevant studies. We contacted corresponding authors, field experts, and companies manufacturing calcium phosphate (Synthes, Paoli, Pennsylvania; Stryker, Kalamazoo, Michigan; DePuy, Warsaw, Indiana) to provide additional potentially relevant studies. We conducted our electronic search in three stages. In the first stage, two of us (S.S.B. and A.L.) reviewed the titles and, if the title suggested any possibility that the article might meet eligibility criteria, we retrieved the abstract. In the second stage, we reviewed the abstracts and chose potentially eligible studies for retrieval of the full text. In the third stage, we checked the full-text articles for eligibility criteria. When the same data were reported in more than one article, only the article with the most complete data set was included and the duplicate publication was eliminated.

Assessment of Study Quality

Two of us (S.S.B. and A.L.) independently assessed the methodological quality of each included study with respect to the method of random sequence generation, allocation concealment, baseline comparability, similarity of care programs, blinding of patients and outcome assessors, statement of primary outcome, sample size calculation, statistical analysis, and the proportion of patients who had been lost to follow-up. In addition, the two of us used the Detsky scale to grade the quality of reporting of published studies\textsuperscript{15}. This scale grades the reporting of studies on the basis of eligibility criteria, the adequacy of randomization, the description of therapies, the assessment of outcomes, and statistical analysis. In both cases, we resolved disagreements by means of discussion to achieve consensus.

Data Extraction

For each eligible study, two of us (S.S.B. and A.L.) independently extracted relevant data and checked the accuracy. Specifically, we abstracted the number of participating centers, the country where the trial was centered, the type of fracture, the type of calcium phosphate cement, the inclusion and exclusion criteria, the sample sizes of the intervention and control groups, de-
mographic data (age and gender), the intervention and control protocols, the duration of the study, the rate of loss to follow-up, the study outcomes measured (including clinical outcomes [pain or impairment], radiographic outcomes [fracture-healing or subsidence], and complications [infection]), and the source of funding. The reviewers resolved disagreements by means of discussion to achieve consensus. In addition, we contacted the corresponding author of each eligible study to verify the accuracy of our data abstraction as well as to provide additional information that had not been reported in the published studies.

### Assessing Reviewer Agreement

Kappa, a measure of chance-corrected agreement, provided most estimates of agreement among reviewers for the titles, abstracts, and methods sections of potentially relevant articles. Donner and Klar\(^1^6\) and Fleiss\(^1^7\) provided persuasive arguments favoring the use of this statistic over other measures of agreement. For variables with more than two categories, we used weighted kappa with quadratic weights. For continuous variables, we chose quantitated agreement with use of an intraclass correlation coefficient that yields identical values to weighted kappa with quadratic weights. We chose an a priori criterion of \(\kappa \geq 0.65\) for adequate agreement\(^1^8\). We calculated the kappa for the initial agreement, and any disagreement was resolved by means of discussion.

### Data Synthesis

For each study, we calculated the relative risks and relative risk reductions (with 95% confidence intervals) for dichotomous

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>No. of Centers, Country</th>
<th>No. of Patients*</th>
<th>No. of Female Patients (Intervention Group, Control Group)</th>
<th>Age (Intervention Group, Control Group)† (yr)</th>
<th>Population (Type of Fracture, Age Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kopylov(^2^5, 4^0), 1999</td>
<td>1, Sweden</td>
<td>40 (20, 20)</td>
<td>18, 18</td>
<td>69, 66</td>
<td>Distal radial, 50 to 80 years</td>
</tr>
<tr>
<td>Sanchez-Sotelo(^2^8), 2000</td>
<td>1, Spain</td>
<td>110 (55, 55)</td>
<td>48, 49</td>
<td>65, 67</td>
<td>Distal radial, 50 to 85 years</td>
</tr>
<tr>
<td>Jeyam(^2^3), 2002</td>
<td>1, United Kingdom</td>
<td>18 (9, 9)</td>
<td>9, 9</td>
<td>71, 74</td>
<td>Distal radial, &gt;60 years</td>
</tr>
<tr>
<td>Kopylov(^2^4), 2002</td>
<td>1, Sweden</td>
<td>20 (9, 11)</td>
<td>9, 11</td>
<td>65, 67</td>
<td>Distal radial, 50 to 80 years</td>
</tr>
<tr>
<td>Cassidy(^2^1), 2003</td>
<td>23, United States</td>
<td>323 (161,162)</td>
<td>129, 143</td>
<td>64, 64</td>
<td>Distal radial, ≥45 years</td>
</tr>
<tr>
<td>Dickson(^2^2), 2002</td>
<td>3, United States</td>
<td>40 fractures (21, 19)</td>
<td>7, 6</td>
<td>45, 40</td>
<td>Multiple metaphyseal types, 18 to 80 years</td>
</tr>
<tr>
<td>Mattsson(^2^6), 2003</td>
<td>1, Sweden</td>
<td>40 (20, 20)</td>
<td>18, 15</td>
<td>78, 78</td>
<td>Low-energy femoral neck, 62 to 92 years</td>
</tr>
<tr>
<td>Zimmermann(^2^9), 2003</td>
<td>1, Austria</td>
<td>52 (26, 26)</td>
<td>26, 26</td>
<td>63, 57</td>
<td>Distal radial, menopausal women</td>
</tr>
<tr>
<td>Mattsson(^2^7), 2004</td>
<td>1, Sweden</td>
<td>26 (14, 12)</td>
<td>12, 10</td>
<td>84, 82</td>
<td>Unstable trochanteric††</td>
</tr>
<tr>
<td>Russell(^3^3), 2004#</td>
<td>12, United States, Canada</td>
<td>120 fractures (82, 38)</td>
<td>Overall, 46</td>
<td>43, 43</td>
<td>Tibial plateau, 16 to 77 years</td>
</tr>
<tr>
<td>Larsson(^3^2), 2004#</td>
<td>1, Sweden</td>
<td>26 (13, 13)**</td>
<td>Not reported</td>
<td>50, 52</td>
<td>Tibial plateau, 16 to 60 years**</td>
</tr>
<tr>
<td>Mattsson(^3^0), 2005</td>
<td>3, Sweden</td>
<td>112 (55, 57)</td>
<td>44, 47</td>
<td>81, 82</td>
<td>Unstable trochanteric††, &gt;65 years</td>
</tr>
<tr>
<td>Mattsson(^3^1), 2006</td>
<td>1, Sweden</td>
<td>118 (58, 60)</td>
<td>46, 49**</td>
<td>77, 77**</td>
<td>Displaced femoral neck, &gt;60 years</td>
</tr>
<tr>
<td>Reed(^3^5), 2005#</td>
<td>1, Canada</td>
<td>48 fractures (21, 27)**</td>
<td>1, 1**</td>
<td>36, 37**</td>
<td>Displaced calcaneal, &gt;16 years</td>
</tr>
</tbody>
</table>

*The values are given as the total number of patients in the study, with the numbers of patients in the intervention and control groups in parentheses. †The values are given as the mean. †ORIF = open reduction and internal fixation. §SF-36 = Short Form-36; DASH = Disabilities of the Arm, Shoulder and Hand; LEM = Lower Extremity Measure. #Abstract. **Author contact. ††Intertrochanteric fractures in the North American literature.
outcomes (the number of patients in the intervention and control groups with pain, impairment of function, fracture healing, loss of reduction, and infection) and mean differences (with 95% confidence intervals) for continuous outcomes (the mean difference between the intervention and control groups with regard to grip strength, range of motion, and radiographic parameters). When possible, we pooled data across studies with use of relative risks, relative risk reductions, the number needed to treat for dichotomous outcomes, and the weighted mean differences for continuous outcomes. Our rationale for statistical pooling included (1) a similarity of point estimates of treatment effects with widely overlapping confidence intervals across studies resulting in nonsignificant tests of heterogeneity across studies and (2) a belief that across the populations, interventions, and outcomes, we could expect, more or less, the same direction of treatment effect.

Given the potential diversity of included studies, we used a conservative method of statistical pooling, the random-effects model. This model assumes that the studies included in the meta-analysis are a random sample of a population of studies addressing the question posed. It takes into account both within-study and between-study variability. We assessed heterogeneity among studies with use of the Cochrane’s $\chi^2$ value and reported the $p$ value and the $I^2$ value as proposed by Higgins and Thompson. We used Review Manager 4.2.8 (The Cochrane Collaboration) for statistical analysis and graphical output. We conducted funnel plots to test for publication bias by plotting the study sample size against the magnitude of treatment effect (relative risk or weighted mean difference). In the absence of publication bias, the plot should resemble a symmetrical inverted funnel.

### Evaluation of Heterogeneity

We defined study heterogeneity as a significant Cochrane’s $\chi^2$ test of heterogeneity ($p < 0.1$). We used a lower-than-conventional threshold of significance because tests of heterogeneity are typically underpowered. We identified, a priori, hypotheses regarding potential sources of heterogeneity in the

<table>
<thead>
<tr>
<th>Fracture Treatment (Intervention Group/Control Group)†</th>
<th>Major Outcome Measures§</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed reduction, Norian, and cast/closed reduction and external fixation</td>
<td>Pain, range of motion, grip strength, radiographic parameters, radiostereometric analysis</td>
<td>Industry and peer-reviewed</td>
</tr>
<tr>
<td>Closed reduction, Norian, and cast/closed reduction and cast</td>
<td>Pain, range of motion, grip strength, radiographic parameters, malunion</td>
<td>Not reported</td>
</tr>
<tr>
<td>Closed reduction, BoneSource, and cast/closed reduction, Kirschner wires, and cast</td>
<td>Range of motion, grip strength, radiographic parameters</td>
<td>Industry</td>
</tr>
<tr>
<td>Closed reduction, Norian, and cast/retain original cast (no reduction)</td>
<td>Pain, range of motion, grip strength, radiographic parameters</td>
<td>Industry and peer-reviewed</td>
</tr>
<tr>
<td>Closed reduction, Norian, and either cast or external fixation ± Kirschner wires/closed reduction and either cast or external fixation ± Kirschner wires</td>
<td>Pain, range of motion, grip strength, radiographic parameters, loss of reduction, SF-36</td>
<td>Industry</td>
</tr>
<tr>
<td>BoneSource/autogenous iliac crest bone graft</td>
<td>Pain, regain of function, fracture-healing, loss of reduction</td>
<td>Industry</td>
</tr>
<tr>
<td>Closed reduction, two screws, and Norian/closed reduction and two screws</td>
<td>Radiostereometric analysis</td>
<td>Industry</td>
</tr>
<tr>
<td>Closed reduction, Norian, Kirschner wires, and cast/closed reduction, Kirschner wires, and cast</td>
<td>Range of motion, grip strength, radiographic parameters, fracture-healing, DASH</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dynamic hip screw and Norian/dynamic hip screw</td>
<td>Radiostereometric analysis</td>
<td>Industry</td>
</tr>
<tr>
<td>ORIF and α-BSM/ORIF and autogenous iliac crest bone graft</td>
<td>Range of motion, fracture-healing, loss of reduction</td>
<td>Industry</td>
</tr>
<tr>
<td>ORIF and Norian/ORIF and autogenous iliac crest bone graft</td>
<td>Pain, weight-bearing, radiostereometric analysis, Lysholm knee score</td>
<td>Industry and peer-reviewed</td>
</tr>
<tr>
<td>Dynamic hip screw and Norian/dynamic hip screw</td>
<td>Pain, activities of daily living functions, muscle strength, SF-36, radiographic parameters</td>
<td>Industry and peer-reviewed</td>
</tr>
<tr>
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<td>Pain, activities of daily living functions, muscle strength, radiographic parameters</td>
<td>Industry and peer-reviewed</td>
</tr>
<tr>
<td>ORIF and α-BSM/ORIF</td>
<td>Radiographic parameters, SF-36, LEM score</td>
<td>Industry</td>
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</tbody>
</table>

#### TABLE I (continued)

<table>
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</tr>
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<td>Closed reduction, Norian, and cast/closed reduction and cast</td>
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<td>Not reported</td>
</tr>
<tr>
<td>Closed reduction, BoneSource, and cast/closed reduction, Kirschner wires, and cast</td>
<td>Range of motion, grip strength, radiographic parameters</td>
<td>Industry</td>
</tr>
<tr>
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<td>Pain, range of motion, grip strength, radiographic parameters</td>
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<td>Range of motion, grip strength, radiographic parameters, fracture-healing, DASH</td>
<td>Not reported</td>
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<td>Industry</td>
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</table>
We hypothesized that heterogeneity might be due to differences in the type of control group (autogenous bone graft or no graft), the type of fracture (radial, tibial, femoral, or multiple), and study quality score (<70% or ≥70%). We hypothesized that studies involving the use of autogenous bone graft in the control group would demonstrate less significant differences in pain, functional impairment, fracture-healing, subsidence, and infection rate between the intervention and control groups than would studies that involved the use of no graft in the control group. Similarly, we hypothesized that studies with higher quality scores would have less significant differences than those with lower quality scores. With regard to fracture type, we hypothesized that studies involving fractures of the non-weight-bearing upper extremity (distal radial fractures) would demonstrate less significant differences in terms of treatment effects with regard to pain, functional impairment, fracture-healing, and subsidence between the intervention and control groups than would studies involving fractures of the lower extremity (femoral and tibial fractures).

Results

Study Identification

Our three stages of search eliminated all but twenty-three of 526 potentially relevant citations. Of the twenty-three included citations, eleven were published randomized controlled trials, four were abstracts of three unpublished randomized controlled trials that had been presented at international meetings, four were abstracts of three of the included published randomized controlled trials that had been presented at international meetings, one reported on a different outcome for a subset of patients who had been involved in an included published randomized controlled trial, one reported the early results for a subset of patients who had been involved in an included published randomized controlled trial, one was a report of an early experience, and one was a Spanish-language version of an included English-language study. Thus, fourteen randomized controlled trials (including eleven full-text articles and three abstracts) proved to be eligible for inclusion in the present systematic review. Figures E1-A and E1-B in the Appendix summarize the literature search flow.
weighted kappa coefficient on the initial agreement of the included citations was 0.85. Disagreement was resolved with discussion and consensus. We obtained responses from five authors 24, 26, 32, 33, 35. All authors of the three included abstracts provided their full manuscript 32, 33, 35.

**Study Characteristics**

The characteristics of the included studies are summarized in Table I. Of the fourteen studies, six involved fractures of the distal part of the radius 21, 23-25, 28, 29, two involved fractures of the femoral neck 26, 31, two involved unstable femoral trochanteric fractures (“intertrochanteric” fractures in the North American literature) 27, 30, one involved multiple types of metaphyseal fractures 22, and one involved fractures of the calcaneus 35. Only four studies were multicenter trials 21, 22, 30, 33. The total number of fractures was 1179. Ten studies were conducted in a European country 23-32, and four were conducted in a North American country 21, 22, 33, 35. The type of calcium phosphate used was Norian SRS (Skeletal Repair System) (monocalcium phosphate monohydrate, calcite, alpha-tricalcium phosphate) (Synthes, Paoli, Pennsylvania) in ten studies 21, 24-32, BoneSource (dicalcium phosphate anhydrous, tetracalcium phosphate) (Stryker, Kalamazoo, Michigan) in two 22, 25, and alpha-BSM (dicalcium phosphate dehydrate, alpha-tricalcium phosphate) (DePuy, Warsaw, Indiana) in two 33, 35. Autogenous iliac crest bone graft was used in the control group in three studies 22, 32, 33; in the other eleven studies, no grafting was performed. The funding source was reported to be industry in seven studies 21-23, 26, 27, 33, 35; and industry and peer-reviewed organizations in five studies 24, 25, 30-32; the funding source was not reported in two studies 28, 29.

**Study Quality**

The methodological quality of the included studies is summarized in Table II. All studies were randomized controlled trials. Only one study 22 reported the method of random sequence generation. Additional information regarding the type of randomization was obtained for seven additional studies by contacting the authors 24, 25, 30-33, 35. While the method of allocation concealment was not reported in four studies, the method of concealment was reported to be sealed envelopes in nine other studies 21, 22, 24-27, 30-33, 35. Blinding of the patients was not reported in any study. The study by Reed et al. was the only study in which the outcome assessors were partially blinded 35. Calcium phosphate cement is radiodense, and therefore it is impossible to blind the outcome assessors; in the study by Reed and colleagues, the radiologists were blinded to the follow-up interval.
The inclusion criteria were reported in all studies, and the exclusion criteria were reported in eleven. Four studies had differences in baseline characteristics that were not adjusted for in the final analysis, which could bias the results and limits the generalizability of the findings. Sample-size calculation and specification of the primary outcome were reported in eight studies. Post-randomization exclusions were reported in three studies, in which the statistical analysis conducted was per-protocol. The percentage of patients who had complete study follow-up ranged from 31% to 100%. The Detsky score of the quality of reporting was transformed to percentage for ease of reporting. We determined an arbitrary cut-off point of study quality of 70%. Seven of fourteen studies scored ≥70%. We conducted sensitivity analysis on the basis of the quality of the study (Detsky score) for each outcome to study the causes of potential heterogeneity between the studies.

**Pain**
The results of statistical pooling are summarized in Table III. Of the fourteen studies, eight evaluated the outcome with regard to pain. Three of these presented the data categorically (i.e., the number of patients with no pain, mild pain, moderate pain, and severe pain), and five presented...
the data as a continuous outcome (i.e., as a mean pain score based on a visual analog scale)\textsuperscript{21,22,28,32}. It was not possible to transform either form into the other. We included the pain data from the three studies that used a categorical outcome (n = 455 patients)\textsuperscript{21,22,28}. The data from the five studies that used a continuous outcome were not included, because three of the five studies did not include the standard deviation, which limits the ability of statistical pooling. The categorical presentation was dichotomous (present or absent) in two studies\textsuperscript{21,22} and ordinal (mild, moderate, or severe) in one study\textsuperscript{28}. We collapsed the ordinal categories into dichotomous categories (present or absent) in order to allow pooling across the studies. Of the three studies from which we were able to pool the pain outcomes, only one involved the use of autogenous iliac crest bone graft in the control group\textsuperscript{22}. Pain at the iliac crest graft harvest site is a potential confounder for pain assessment. However, Dickson et al. showed no pain at the graft harvest site in any patient at six and twelve-month follow-up visits\textsuperscript{22}. Hence, we pooled all of the pain outcomes of the fracture site across the three studies\textsuperscript{21,22,28}.

There was a lower prevalence of pain at the fracture site in the intervention group (n = 455 patients) (relative risk, 0.57 [95% confidence interval, 0.33 to 0.99]; relative risk reduction, 43% [95% confidence interval, 1% to 67%]; p = 0.04; heterogeneity tests, p = 0.39, I\textsuperscript{2} = 0%). Although tests for heterogeneity were nonsignificant, we conducted sensitivity analyses to test our hypotheses. The sensitivity analysis by the type of control group showed that the calcium phosphate group had more significant pain control when the control group used no bone graft\textsuperscript{21,22,28} compared with a nonsignificant difference in pain control in the calcium phosphate group when the control group used autogenous iliac crest bone graft\textsuperscript{22} (relative risk, 0.44 [95% confidence interval, 0.23 to 0.86] [p = 0.02] compared with 0.96 [95% confidence interval, 0.38 to 2.46] [p = 0.94]) (see Appendix, Fig. E-2A). This translates into a relative risk reduction of 56% (95% confidence interval, 14% to 77%) in the prevalence of pain when the use of calcium phosphate was compared with the use of no grafting material. Therefore, for every sixteen patients managed with calcium phosphate, one episode of postoperative pain could be averted (number needed to treat, 16). Studies of fractures of the less-weight-bearing upper extremity (the distal part of the radius)\textsuperscript{21,28} demonstrated a more significant difference in terms of pain in favor of calcium phosphate cement than did studies of fractures of the weight-bearing lower extremity\textsuperscript{22} (relative risk, 0.44 [95% confidence interval, 0.23 to 0.86], p = 0.02; relative risk reduction, 56% [95% confidence interval, 14% to 77%]; number needed to treat, 16) (see Appendix). There was no significant difference in treatment effect in association with study quality (relative risk, 0.65 [95% confidence interval, 0.31 to 1.33] [p = 0.24] for lower-quality studies, compared with 0.40 [95% confidence interval, 0.13 to 1.26] [p = 0.12] for higher-quality studies).

**Functional Outcome**

A functional outcome measure was reported in five of the fourteen studies. The outcome measure was categorical in one study\textsuperscript{22} and continuous in four\textsuperscript{21,29,30,33}; in the latter group, the SF-36 (Medical Outcome Study 36-Item Short Form) was used in three studies\textsuperscript{21,29,30}, and the DASH (Disabilities of the Arm, Shoulder and Hand) was used in one\textsuperscript{29}. One of the three studies that involved the SF-36 did not provide the actual results\textsuperscript{21} and the other two did not provide standard deviations\textsuperscript{30,33}, so data-pooling was not feasible for the continuous outcome. Three of those five studies demonstrated significantly improved functional scores in association with the use of calcium phosphate\textsuperscript{21,29,30}. In contrast, Dickson et al. found a difference in functional impairment in favor of the use of iliac crest bone graft\textsuperscript{22}; however, the difference was not significant (relative risk, 5.8 [95% confidence interval, 0.77 to 43.5], p = 0.09). In the three studies in which the SF-36 was used as an outcome measure, one demonstrated no significant differences between the study and control groups in terms of any of the eight SF-36 subsdomains\textsuperscript{22}, whereas two demonstrated significantly better scores for the calcium phosphate group; specifically, Cassidy et al. found significantly higher scores (representing better function) in the “bodily pain,” “role physical,” “role emotional,” “social functioning,” and “mental health” subsdomains\textsuperscript{22}, and Mattsson et al. found higher scores in the “physical functioning,” “vitality,” “social functioning,” “mental health,” and “general health” subsdomains\textsuperscript{30}. Zimmermann et al. found significantly better DASH scores for the calcium phosphate group\textsuperscript{22}.

Given the few outcome measures for which we were able to pool across studies, we explored the possibility of pooling across other surrogate measures of function (e.g., range of motion and grip strength). These data were reported for distal radial fractures only. The results are summarized in Table III.

**Fracture-Healing**

Four studies (n = 216 patients) evaluated fracture-healing at one year\textsuperscript{22,29,32,33}. In all studies, all fractures healed in both the calcium phosphate and control groups.

**Loss of Fracture Reduction**

Five studies (n = 599 patients) evaluated outcome with regard to the loss of reduction\textsuperscript{21,22,28,32,33}. Point estimates suggested that the use of calcium phosphate reduced the prevalence of loss of fracture reduction as compared with that in controls; however, this difference was not significant (n = 599; relative risk, 0.54 [95% confidence interval, 0.26 to 1.13], p = 0.10; heterogeneity p = 0.01, I\textsuperscript{2} = 69%).

We conducted sensitivity analyses to explore causes of heterogeneity. Calcium phosphate reduced the risk of loss of reduction compared with autogenous bone graft by 68% (n = 166, relative risk, 0.32 [95% confidence interval, 0.14 to 0.70], p < 0.001; relative risk reduction, 68% [95% confidence interval, 30% to 86%]; number needed to treat, 6; heterogeneity, p = 0.87, I\textsuperscript{2} = 0%) (see Appendix); in patients with tibial plateau fractures (relative risk, 0.3 [95% confidence interval, 0.13 to 0.72], p = 0.007; relative risk reduction, 70% [95% confidence interval, 28% to 87%]; number needed to treat, 6; heterogeneity, p = 0.64, I\textsuperscript{2} = 0) (see Appendix); and in studies with lower-quality scores (rel-
ative risk, 0.38 [95% confidence interval, 0.23 to 0.63], \( p = 0.0002 \); relative risk reduction, 62% [95% confidence interval, 37% to 87%]; heterogeneity, \( p = 0.74, I^2 = 0\% \). Inverted funnel plots did not suggest publication bias.

We attempted to pool secondary radiographic outcomes (radiographic analysis of the distal part of the radius and radiostereometric analysis measurement) across four studies (n = 492 patients) (Table III)[21,22,29,31, 33,35]. However, study heterogeneity was high (\( I^2 = 79\% \) to 100%), and therefore inferences based on this analysis are limited.

**Infection**

Seven studies (n = 718 patients) provided details regarding infection following surgery[21,22,29,31, 33,35]. All studied outcomes were dichotomous (the presence or absence of infection). There was no significant difference in the prevalence of infection between the calcium phosphate bone cement group and the control group (relative risk, 0.74 [95% confidence interval, 0.19 to 2.87], \( p = 0.66 \); heterogeneity, \( p = 0.03, I^2 = 59\% \)). We conducted sensitivity analyses to explore the sources of heterogeneity. There was no significant difference in the prevalence of infection regardless of the type of control group or the quality of the study. However, the use of calcium phosphate significantly reduced the risk of infection in patients with distal radial fractures (relative risk, 0.15 [95% confidence interval, 0.15 to 0.42], \( p < 0.0001 \); relative risk reduction, 85% [95% confidence interval, 58% to 85%]).

**Discussion**

**Summary of Findings**

Our meta-analysis confirmed that the use of calcium phosphate bone cement for the treatment of fractures is associated with the benefits of (1) less pain at the fracture site compared with that in controls managed with no bone graft or no bone-graft substitutes, and (2) a reduced risk of losing fracture reduction when compared with autogenous bone graft, especially in patients with tibial plateau fractures. Since the pooling of the loss of reduction outcome across five studies [21,22,29,31,35] revealed no statistical difference between the calcium phosphate bone group cement and the control group with significant heterogeneity (\( I^2 = 69\% \)), the sensitivity analysis revealed that the heterogeneity is potentially due to the differences in the control group and the differences in the fracture type. The analysis showed that the risk of loss of reduction was significantly lower in the calcium phosphate bone cement group than in the autogenous iliac crest bone graft group. Similarly, it showed that the risk of loss of reduction was significantly lower in patients with tibial plateau fractures as compared with other types of fractures.

Although we were not able to pool the functional outcomes across the studies, the results of individual studies suggested improved functional outcomes in association with the use of calcium phosphate cement. This finding could be explained by the fact that patients in the calcium phosphate group had less pain and less risk of loss of reduction.

There was no significant difference in the prevalence of infection between the calcium phosphate bone cement group and the control group. Sensitivity analysis showed that, among individuals with radial fractures, the rate of infection was significantly lower among patients who were managed with calcium phosphate bone cement than in controls who were managed with no bone graft substitute. We found no differences in the rates of fracture-healing between the two groups.

**Strengths and Limitations**

Our meta-analysis met accepted standards for the conduct of systematic reviews, including literature search, study selection, validity assessment, and data abstraction, in duplicate and independently, to ensure the reproducibility of the search methodology. We improved the generalizability of the systematic reviews by including studies published in any language. We limited the risk of publication bias by using a very comprehensive search strategy involving multiple data sources, including multiple electronic databases, registers of randomized trials, web sites of major national orthopaedic association meetings, corresponding authors, field experts, manufacturers of calcium phosphate cement, and citation lists. Although the inclusion of unpublished trials in meta-analyses is controversial, we included unpublished studies to avoid the risk of publication bias and subjected them to the same rigorous methodological assessment as was used for the published studies[44,45]. As a final safeguard to limit bias, we developed, a priori, hypotheses and their direction to explain potential sources of heterogeneity of pooled outcomes.

Despite our efforts, limitations exist. We cannot exclude the presence of additional unpublished trials that showed a negative or an equivocal difference between the intervention and control groups. Because of the small number of studies assessing each outcome, we were not able to construct meaningful funnel plots. Some studies had methodological limitations, including small sample sizes and incomplete reporting of treatment allocation concealment. Differences in the care programs between the intervention and control groups in terms of the duration of immobilization and the types of supplemental fixation may limit inferences. Another potential source of bias was the use of different fixation devices or techniques in the intervention and control groups. Finally, although we pooled results from studies that involved the use of different types of calcium phosphate cement, the differences in the chemical composition, mechanical properties, and resorptive properties of the types of calcium phosphate cement limit the generalizability of the findings of this meta-analysis for all products of calcium phosphate cement. Despite differences among the studies, our findings suggest that, across varying implants, product providers, and perioperative care regimes, calcium phosphates consistently lead to improvements in terms of pain and loss of reduction as compared with alternative approaches.

A major difficulty that faces authors of meta-analyses is the inadequacy of reporting of the results of randomized controlled trials, which limits their ability to pool results across trials. The Consolidated Standards of Reporting Trials (CONSORT) Statement is a twenty-two-item checklist of the minimum recommendations for reporting randomized controlled trials developed by the CONSORT Group to alleviate such limitations[46].

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The Use of Calcium Phosphate Bone Cement in Fracture Treatment
This statement was adopted by major journals, which will eventually improve the reporting of randomized trials, and hence, the conduct of meta-analyses.

Relevant Literature
Synthetic bone materials, such as different types of calcium phosphate bone cement, have been used more frequently over the last few years to fill fracture voids. Synthetic materials have the advantages of ready availability and reasonable biological and mechanical characteristics of osseointegration and osteoconduction that make them a promising alternative to autograft. It would appear that, in contained metaphyseal defects, the advantage of osteoinduction provided by autograft is not required to achieve excellent outcomes. More importantly, calcium phosphate bone cement lacks the disadvantage of donor-site morbidity associated with autograft and the disadvantages of potential infection and disease transmission associated with allograft. Although calcium phosphate bone cement lacks the osteoinduction and osteogenesis of autograft and is mechanically weaker than autograft or allograft, promising biomechanical and clinical results have been documented in the literature in multiple studies that have assessed this type of bone cement. The results of this meta-analysis confirm the favorable mechanical properties of calcium phosphate bone cement as used in those studies, which resulted in a lower prevalence of loss of fracture reduction as compared with autograft. Various validated functional outcome measures (SF-36, DASH) have been reported inconsistently; however, the results of three separate studies have suggested improved functional outcome scores in association with the use of calcium phosphate bone cement as compared with no grafting material in the control group. Among patients with distal radial fractures, infection rates were significantly lower when calcium phosphate bone cement was used as opposed to when no graft was used. However, this finding should be interpreted with caution because it was a subgroup analysis and because of the fact that the confidence interval is wide.

Overview
The present meta-analysis of fourteen randomized controlled trials suggested that the use of calcium phosphate bone cement for the treatment of fractures in adult patients is associated with a lower incidence of pain, a decreased risk of losing fracture reduction, lower infection rates in patients with radial fractures, and likely improved functional outcomes.

The methodological limitations of the available studies and the lack of patient-relevant outcomes (validated functional outcomes and quality-of-life measures) dictate the planning and performance of a sufficiently sized, methodologically sound study with clinically relevant outcome measures. Our meta-analysis provides the best estimate of the effect of calcium phosphate bone cement use in fracture management; however, these beneficial effects of calcium phosphate bone cement should be interpreted with caution until confirmed by large, definitive randomized trials.

Appendix
Figures showing the search strategy and sensitivity analyses of the outcomes of pain and loss of reduction are available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on “Supplementary Material”) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).

References