Orthopaedics & Traumatology: Surgery & Research 103 (2017) 105–109

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Original article

Evaluating augmentation with calcium phosphate cement (chronOS Inject) for bone defects after internal fixation of proximal tibial fractures: A prospective, multicenter, observational study

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ARTICLE INFO

Article history:
Received 24 February 2016
Accepted 17 October 2016

Keywords:
Proximal tibial fractures
Bone defect
Calcium phosphate cement

ABSTRACT

Introduction: Managing subchondral bone defects in proximal tibia fractures after plateau reduction is an important consideration. ChronOS Inject is a recently developed calcium phosphate bone substitute that shows relatively fast osteointegration.
Hypothesis: Using chronOS Inject during internal fixation of proximal tibial fractures provides a satisfactory treatment option that is both clinically and radiologically safe.
Patients and methods: Patients enrolled in this study were treated with chronOS Inject bone void filler, during internal fixation of proximal tibial fractures. Patients were evaluated preoperatively and at 6 weeks, 6 and 12 months postoperative. Radiographic union was assessed using plain films supplemented by CT scans. Pain, function and adverse events were collected at all visits. A total of 36 patients were enrolled in the study and treated according to a predetermined protocol. Seven of the 36 patients (19.4%) were lost to follow-up.
Results: Successful radiographic union was achieved in 27/29 (93.1%) of patients at final follow-up. Articular subsidence of > 2 mm only occurred in one patient. Statistical analysis showed significant improvements both in leg pain and knee function. Progress in knee function was observed in 93.1% (27/29) of patients from 6 weeks to 12 months. No product-related complications were reported.
Conclusions: Successful union was achieved based on radiographic criteria as well as clinical outcomes. When managing bone defects after internal fixation of proximal tibial fractures, the use of chronOS Inject resulted in significant improvement of knee function and reduction of leg pain.
Level of evidence: Level IV, prospective observational study.

1. Introduction

Proximal tibial fractures can occur from relatively low energy mechanisms (such as a fall from standing height), but more often are associated with high-energy trauma [1]. The most important consideration in the treatment of proximal tibial fractures is the restoration of the plateau surface by anatomic reduction. However, restoration of the plateau surface frequently results in large metaphyseal cancellous bone defects [2]. These subchondral defects must be filled to prevent the joint surface from subsiding when the bone is subjected to loading [3]. Autogenous iliac bone grafts are the most frequently recommended treatment for defects associated with proximal tibial fractures [3]. Despite the widespread acceptance of this procedure, there is significant donor site morbidity and the bone graft typically provides limited stability [4,5].

Calcium phosphate is an injectable, moldable and biocompatible bone substitute that has been effectively used as synthetic bone void filler. Several studies reported successful use of the calcium phosphate bone substitute to fill bone defects in proximal tibial fractures [2,4,6]. Augmenting with calcium phosphate cement was shown to prevent collapse at the fracture site. In addition to mechanical strength, ideal bone substitute should gradually be resorbed over time and replaced by host bone. The rate of calcium phosphate resorption should be balanced with the rate of new bone formation to prevent fragment subsidence [7].

ChronOS Inject (DePuySynthes, Paoli, PA) is a recently developed calcium phosphate bone substitute that was intended to be used as bone void filler for the repair of bone defects caused by

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http://dx.doi.org/10.1016/j.otsr.2016.10.006
1877-0568/

traumatic injury, surgical intervention or bone defect reconstruction. The main benefit of chronOS Inject is rapid osteointegration, which remodels into native bone within 6–18 months. ChronOS Inject has potential utility in internal fixation of proximal tibial fractures. This study evaluated the safety, the radiological and clinical outcomes of patients who underwent internal fixation of proximal tibial fractures using chronOS Inject as bone void filler.

2. Patients and methods

2.1. Patient selection

A prospective, multicenter and observational study was performed in two hospitals. The study protocol was approved by institutional review boards of the respective hospitals and written informed consent was obtained from all patients enrolled in the study. Patients with proximal tibial fractures of type Schatzker I–VI, AO-OTA 41, AO-OTA 42 with bone defects were included [8]. Patients were excluded from the study if they were younger than 18 or had open fractures with severe soft tissue damage, pathologic fractures, active infections, osteopenia or osteoporosis. If dual-energy X ray absorptiometry (DEXA) was required, patients were excluded if DEXA T scores ≤ -1.0. In addition, patients with active rheumatoid arthritis, uncontrolled diabetes mellitus, or any other medical condition(s) that would represent a significant increase in surgical risk or interfere with normal healing were excluded. A total of 36 patients were enrolled from March 2010 to September 2011 with 18 subjects from each site. The study was completed on September 2012.

Follow-up rates at 6 weeks, 6 months and 12 months were 94.4% (34/36), 86.1% (31/36) and 80.6% (29/36), respectively. Preoperative patient demographics are presented in Table 1. Most of the fractures were associated with a high-energy mechanism (23, 63.9%), and more than half of the patients (22, 61.1%) were involved in a traffic accident (motorcycle, car or pedestrian). The prevalence of different fracture types, based on the Schatzker and AO-OTA classification systems are described in Table 2.

Table 1
Baseline demographics for patients with proximal tibial fractures ($n = 36$).

Variables	Value
Age at time of surgery (years)	55.4 ± 14.6
Sex (number of patients, %)	
Female	15 (41.7%)
Male	21 (58.3%)
Height (cm)	163.4 ± 8.99
Weight (kg)	62.6 ± 12.15
Body mass index (kg/m^2)	23.3 ± 3.67
Smoking status (number of patients, %)	
Never	23 (63.9%)
Former	4 (11.1%)
Current	9 (25.0%)

Mean ± standard deviation.

Table 2
Fracture type ($n = 36$).

	n (%)
Schatzker Type I	1 (2.8%)
Schatzker Type II	14 (38.9%)
Schatzker Type III	0 (0.0%)
Schatzker Type IV	2 (5.6%)
Schatzker Type V	6 (16.7%)
Schatzker Type VI	10 (27.8%)
AO-OTA 41	29 (80.6%)
AO-OTA 42	0 (0.0%)

Patients could have more than one fracture type. The number of patients treated was used as the denominator to compute all percentages.

2.2. Operative technique

Surgery was performed by one surgeon at each institution using open reduction and internal fixation. Plate fixation was followed by filling of bone voids with chronOS Inject in all cases, and additional screw or K-wire fixation was done if further stability was necessary. ChronOS Inject is an artificial bone substitute composed of brushite and β-tricalcium phosphate (β-TCP) granules. The calcium phosphate powder and a sodium hyaluronate solution are combined in a manual mixing system to form a viscous paste that can be injected into the bone voids. When fully hardened, the mixture is a composite material of β-TCP granules with a defined pore structure and a brushite matrix. The biphasic structure of chronOS Inject ensures its function as a matrix and an osseous anchor for the ingrowth of bone cells.

2.3. Patient evaluation & follow-up

In addition to preoperative evaluation, patients were reexamined at 6 weeks (±14 days), 6 months (±30 days) and 12 months (±60 days) postoperatively. Clinical outcomes were evaluated using physical examination (time to ambulation and knee extension range of motion) and patient self-assessments included the Lysholm Knee Scale, Visual Analog Scale (VAS) for leg pain intensity and frequency, and SF-12 health survey. Radiograph evaluations included simple anteroposterior and lateral radiographs. Bone union was defined as the continuity of three cortices, demonstrated in two vertical planes (anteroposterior and lateral). If bone union could not be accurately confirmed by simple radiographs until 12 months postoperatively, computerized tomography (CT) scan was performed. For radiological outcomes, union or nonunion, time to union, and evidence of articular subsidence of ≥ 2 mm were assessed by investigators up to the 12-month postoperative follow-up visit. In addition, absorption rates were calculated from X rays with the INFINITT program (INFINITT, Phillipsburg, NJ). Adverse events were also recorded for all study patients.

SPSS version 18.0 (SPSS Inc., Chicago, IL) was used for statistical analyses. A paired T-test was used to determine the effect of treatment by comparing VAS score and SF-12 scores measured at baseline and at each follow-up visit. Time to union was calculated using the Kaplan-Meier estimator of the survivorship function. Statistical significance was established at P-values < 0.05.

3. Results

3.1. Clinical outcomes

The percentage of patients who reached full weight bearing increased from 0% at 6 weeks to 86.7% (26/30) at 6 months and 100% (29/29) at 12 months postoperatively. The number of patients with a range of motion of at least 120 degrees increased over time, from 14 (43.8%) patients at 6 weeks to 26 (83.9%) at 6 months. At the end of follow-up, 28/29 patients (96.5%) reached a total range of motion of at least 120 degrees. Patients regaining full extension also increased over time, with 26/29 (89.7%) achieving full extension at the last follow-up and 3/29 (10.3%) with an extension between 0 and 10 degrees.

When evaluating the Lysholm Knee Scores, the number of patients who graded their postoperative knee function as being "excellent" or "good" increased from 4 (11.8%) at 6 weeks to 23 (74.2%) at 6 months and 25 (86.2%) at 12 months. At the final follow-up visit, only one patient reported "poor" knee function (3.4%). In total, 27/29 patients (93.1%) reported an increased knee function from 6 weeks to 12 months postoperatively (Table 3).

Table 3
The results of Lysholm Knee Scores.

	Week 6 (n = 34)	Month 6 (n = 31)	Month 12 (n = 29)
Excellent (95–100)	1 (2.9%)	8 (25.8%)	14 (48.3%)
Good (84–94)	3 (8.8%)	15 (48.4%)	11 (37.9%)
Fair (65–83)	16 (47.1%)	3 (9.7%)	3 (10.3%)
Poor (<65)	14 (41.2%)	5 (16.1%)	1 (3.4%)

Maximum Lysholm Knee Scores is 100 (based on 8 questions).

Table 4
VAS leg pain intensity and frequency scores (mm).

	VAS leg pain intensity scores		VAS leg pain frequency scores	
	Value	P-value[a]	Value	P-value[a]
Baseline (n = 36)	61.19 ± 32.714		57.28 ± 33.505	
Week 6 (n = 34)	36.43 ± 23.375	0.0011	42.6 ± 27.026	0.0397
Month 6 (n = 31)	32.05 ± 25.692	<0.0001	31.45 ± 25/007	<0.0001
Month 12 (n = 29)	17 ± 18.592	<0.0001	20.52 ± 20.051	<0.0001

Mean ± standard deviation. Note: a score of "0" on the Visual Analog Scale for pain represents no pain while "100" represents the worst possible pain.

[a] Paired t-test were used to evaluate the significance of the change from baseline within the treatment group.

Both VAS leg pain intensity and frequency scores were significantly improved at each follow-up visit compared to baseline scores (Table 4).

For SF-12 scores, a significant improvement from baseline was observed in physical composite score (PCS) 12 months postoperatively (P = 0.0166). Mental Composite Score did not significantly improve over time (Table 5).

3.2. Radiological outcomes

At 6 months postoperative, 27 of 31 assessed patients (87.1%) achieved fracture union at the site of chronOS Inject implantation

Table 5
SF-12 scores.

	Physical composite score (PCS)		Mental composite score (MCS)	
	Value	P-value[a]	Value	P-value[a]
Baseline (n = 36)	37.02 ± 9.616		46.3 ± 9.707	
Week 6 (n = 34)	33.62 ± 8.052	0.7790	47.75 ± 9.624	0.1642
Month 6 (n = 31)	38.92 ± 5.709	0.0656	44.82 ± 8.757	0.9451
Month 12 (n = 29)	42.43 ± 4.589	0.0166	46.45 ± 7.145	0.3785

Mean ± standard deviation. Note: a positive change (post surgery minus baseline) indicates an improvement in the SF-12 measurement.

[a] Paired t-tests were used to evaluate the significance of the change from baseline within the treatment group.

(five of the original patients were lost to follow-up). At 12 months, 27 of 29 assessed patients (93.1%) achieved union (2 additional patients were lost to follow-up) (Fig. 1). Two patients with nonunion at 12 months were reported to be current smokers. Additionally, both patients were involved in high-energy accidents leading to Schatzker type V fractures. One of the patients with nonunion was treated with an autogenous cancellous bone grafting procedure 11.5 months after the initial surgery.

Mean time to union was calculated to be 7.5 months (SD = 0.0441). No evidence of articular subsidence ≥ 2 mm was found at 6 weeks while one patient showed evidence at 6 months that lasted throughout the 12-month visit (Table 6). Next to the region of articular subsidence, this patient exhibited a loss of reduction and a depression of the lateral condyle of the tibia.

Regarding the absorption rate and time to absorption of the calcium phosphate cement, 14% of the cement was absorbed after 6 weeks, 37% at 6 months and 64% at 12 months.

3.3. Adverse events

Neither microscopic nor radiologic cement leakage was observed during the procedure. During the perioperative period,

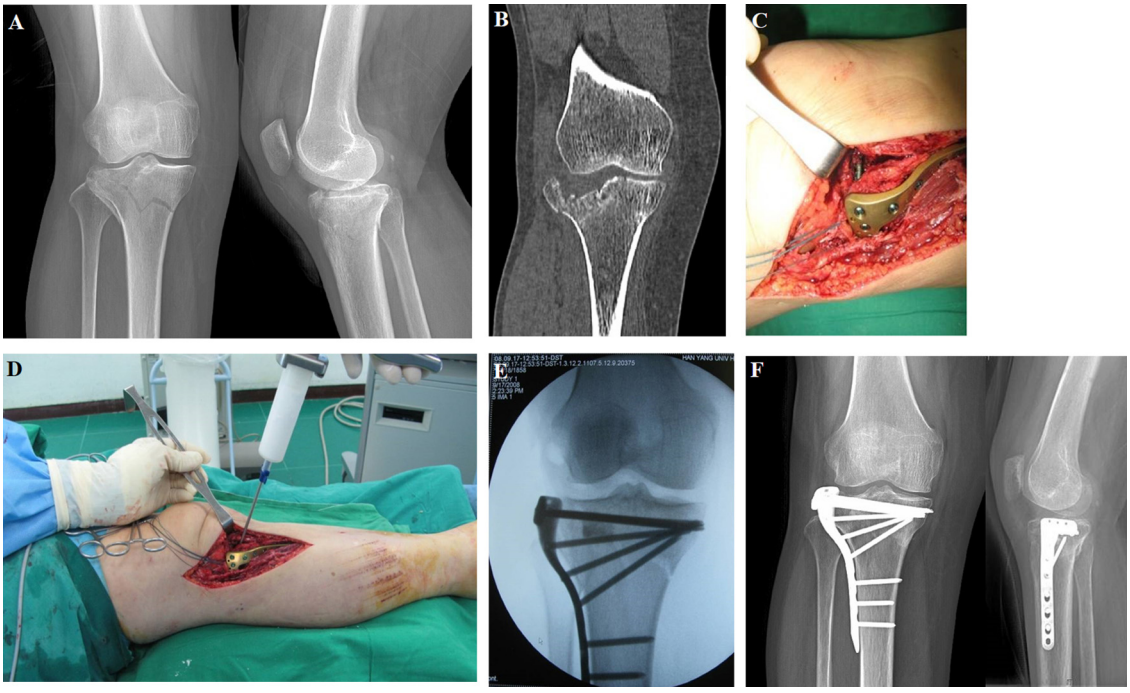

Fig. 1. A. Radiographs of the knee of a 45-year-old woman showing proximal tibial fracture with depression after a severe fall. B. Two-dimensional computerized tomography demonstrating the depression of the lateral plateau. C. Accurate reduction of the plateau surface was achieved using a submeniscal approach, and then internal fixation with a plate and screws was performed. D. For large cancellous bone defects resulting from reduction of impacted fragments, chronOS Inject was used to fill the defect to prevent the joint surface from subsidence. E. Intraoperative radiography after open reduction and internal fixation (ORIF) with plate and injection of chronOS Inject. F. Six months postoperatively, complete bone union was achieved without any complications.

Table 6
Subject-specific radiographic outcomes.

Patient	Radiographic union			Articular subsidence (≥2 mm)
	Week 6	Month 6	Month 12	
1	No union	Union	Union	Absent
2	No union	Union	Union	Absent
3	No union	Union	Union	Present
4	No union	Union	Union	Absent
5	No union	Union	Union	Absent
6	No union	Union	Union	Absent
7	No union	Union	Union	Absent
8	No union	Union	Union	Absent
9	No union	No data available	No data available	No data available
10	No union	Union	Union	Absent
11	No union	Union	Union	Absent
12	No union	Union	Union	Absent
13	No union	No union	No union	Absent
14	No union	Union	Union	Absent
15	No data available	No data available	No data available	No data available
16	No union	Union	Union	Absent
17	No union	No data available	No data available	No data available
18	No union	Union	Union	Absent
19	No union	Union	Union	Absent
20	No union	Union	Union	Absent
21	No union	Union	Union	Absent
22	No union	Union	Union	Absent
23	No union	Union	Union	Absent
24	No union	Union	Union	Absent
25	No data available	No union	Union	Absent
26	No union	Union	Union	Absent
27	No union	Union	Union	Absent
28	No union	No union	No data available	No data available
29	No union	Union	Union	Absent
30	No union	Union	No data available	No data available
31	No union	No union	No union	Absent
32	No union	No data available	No data available	No data available
33	No union	Union	Union	Absent
34	No union	Union	Union	Absent
35	No union	Union	Union	Absent
36	No data available	No data available	No data available	No data available

none of the fixing devices broke, no surgical site infections occurred and no patients required reoperation during their hospital stay. Three patients underwent secondary surgery at the trauma site for irritation caused by K-wires (2 cases) and nonunion (1 case). No adverse events related to chronOS Inject were reported in this study.

4. Discussion

Despite the number of treatment options, management of patients with proximal tibial fractures remains a treatment challenge for orthopedic surgeons. After achieving adequate reduction, stable fixation of the proximal fragment is mandatory. Large metaphyseal bone defects resulting from elevating the depressed articular fragment cause secondary fragment displacement if the proximal fragment is not sufficiently stabilized [3]. Bone graft or suitable substitutes are commonly used to support elevation of depressed segments. Although bone grafting is considered the gold standard treatment for bone defects, it has several disadvantages such as donor site morbidity and limited availability [9].

Different biomaterial alternatives to bone grafts have been developed and widely used. Polymethylmethacrylate (PMMA) cement may be well molded into the defect and provides good strength in patients with osteoporotic fractures [10]. However, its clinical use may be limited due to exothermic reactions during curing, the inability of the cement to be remodeled and the risk of compromising local bone healing due to the interposition of cement between fracture surfaces [7]. Injectable calcium phosphate cements (CPCs), which are susceptible to remodeling and replacement by host bone, have been introduced. CPCs have the advantage of being able to fill complex-shaped bone voids [11]. After injection, calcium phosphate hardens within minutes without generating heat [7].

There are two main types of hydraulic CPCs depending on the end-product of the setting reaction, apatite [$Ca_5(PO_4)OH$] and brushite [$CaHPO_4 2H_2O$]. The apatite CPC has higher mechanical stability and apatite calcium phosphate is naturally found in bone. As a result, this CPC is more widely used and investigated than brushite [2,11,12]. However, brushite CPC is a promising alternative because of its faster resorption time as well as its increase in new bone formation compared to apatite cements [13]. Although several studies reported that apatite CPC was used to fill bone defects in proximal tibial fractures with good success, clinical results of brushite CPC for defect augmentation in proximal tibial fractures is very limited [2,14].

The chronOS Inject is the first available bone void filler based on brushite CPC. Ryf et al. [15] reported that the chronOS Inject resulted in good outcomes in the majority of patients with distal radius and proximal tibial fractures. In our study, good clinical and radiologic outcomes were also achieved using chronOS Inject for augmentation of bone defects in proximal tibial fractures. Significant improvements in leg pain were observed and most patients (93.1%) reported an increased knee function over time. Successful radiographic union was achieved in most patients (93.1%) at final follow-up. Although two patients with nonunion were reported at the end of follow-up, they were current smokers, a well-known risk factor for delayed bone healing, and both were involved in high-energy trauma [16].

One of the most important goals in the use of bone substitute is the prevention of fragment subsidence. There was only

one patient (3.4%) with evidence of articular subsidence ≥ 2 mm in this study. In another study using chronOS Inject for augmentation of bone defects, loss of reduction was identified on radiographs in 4/38 patients (11%) with proximal tibial fractures and 9/37 patients (24%) with distal radius fractures [15]. In some studies using Norian SRS (Norian, Cupertino, CA) based on apatite CPC, loss of reduction has been documented in 8–16% of patients with proximal tibial fractures [2,14]. Compared to previous studies, the incidence of articular subsidence in our study is low. This may have resulted from exclusion of patients with osteopenia or osteoporosis. Although the mechanical properties of chronOS Inject are known to be lower compared to other bone substitutes such as PMMA and apatite CPC, when it is used to fill bone defects in patients with good bone quality, satisfactory outcomes have been demonstrated [13,17,18]. In order to evaluate the clinical use of chronOS Inject in patients with poor bone quality, further studies are needed.

For resorption rate, 64% of the calcium phosphate cement was resorbed after 12 months. Arora et al. [18] reported that 15 months after implantation, the relative amount of chronOS Inject was between 3% and 10% of the total bone volume of that region. In comparison, 41 (84%) of 49 patients using Norian SRS in proximal tibial fracture had little evidence of resorption at 1 year [14]. The cement resorption of brushite CPC is well known to be faster than apatite CPC [13,19]. In sheep bone, brushite matrix showed faster resorption than β-TCP granules [19]. The β-TCP granules serve as an anchor for newly formed trabecular bone. The cement front is immediately followed by newly formed woven bone in direct contact with the not yet resorbed β-TCP granules. Therefore, biphasic brushite cement (chronOS Inject) is potentially advantageous in bone applications [19,20].

Cement leakage is a common complication when using injectable bone void fillers [15]. Cassidy et al. [21] reported that cement leakage within the joint space was observed in 4/161 patients (2.4%) with distal radius fractures but no patients had associated symptoms or clinical sequelae related to intra-articular cement. However, as it is reported in the study by Lobenhoffer el al. [2], one patient had symptomatic intra-articular cement necessitating reoperation. In our study, neither microscopic nor radiological cement leakage was observed. This complication can be prevented by using an injection technique that starts under the chondral surface without any pressure on the cement. Furthermore, no adverse events related to cement were reported during this study, indicating that chronOS Inject is physiologically inert.

This study has several limitations. It is an uncontrolled case series limited to two centers, with a small sample size of 36 subjects. Based on the exclusion criteria of the study, the clinical utility of chronOS Inject in patients with osteoporosis or osteopenia could not be determined. Lastly, the study had a fairly high attrition rate, with seven of the 36 patients (19.4%) not completing the 12–month follow-up visit. This low rate of the follow-up was due to cultural and economic reasons.

Our findings suggest that augmentation of proximal tibia fractures using chronOS Inject provides adequate mechanical support to prevent fragment subsidence and shows a superior resorption rate, with a higher probability of trabecular bone regeneration. Both radiographic and clinical outcomes showed that successful union was achieved. Results from using chronOS Inject for augmentation of bone defects after internal fixation of proximal tibial fractures exhibited significant effectiveness in improving knee function and reducing leg pain.

Disclosure of interest

The authors declare that they have no competing interest.

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