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Plaster of Paris as bone substitute in spinal surgery

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Abstract In order to assess the effectiveness of calcium sulphate (plaster of Paris; POP) as a substitute for autologous bone graft, we performed lumbar intervertebral fusion in mature sheep using POP and a variety of other graft materials, and reviewed the literature. The osteoconductivity of the POP grafts was compared to that of grafts carried out with autogenous iliac crest, frozen allogeneic bone, and ProOsteon 500 coralline bone. We also compared the osteogenicity of POP to admixtures of autogenous iliac crest bone with POP and coralline bone, and to an osteoinductive demineralized sheep bone preparation (DBM). The substrates were loaded into tubular titanium mesh, implanted into excavated disc spaces and recovered after a period of 4 months. Fusion mass segments tested in flexion and tension showed that POP was equal to autogenous bone and most other substrates. The POP fusions were significantly tougher than the DBM fusions, even though histomorphometry failed to reveal differences in the amount of trabecular bone. We conclude that POP can be used to achieve a biomechanically stable interbody lumbar vertebral fusion. In addition, our literature review indicated that POP can be used as a vehicle for local delivery of antibiotics in bone infections.

Keywords Osteoinduction · Osteoconduction · Plaster of Paris · Replamineform coralline · Intervertebral fusion

Introduction

Stabilization of the spinal column is crucial to the preservation of neurologic function, and bone grafting is a prerequisite to obtaining the solid arthrodesis imperative to spinal stability [16]. Bone grafting is also essential for reconstruction of spinal defects and offers a surgical procedure for filling the bone defects caused by infection and tumors.

Early attempts at bone grafting date back more than 500 years to the Arab, indigenous Peruvian, and Aztec cultures. In modern times, the first documented case of autogenous bone grafting was reported by Merem in 1810, and the first successful allografting case has been attributed to Macewn in 1881 [32].

Our present knowledge and scientific base for understanding the biology, banking, and widespread clinical applications of bone grafting is largely due to the work of Albee [1], Barth [2], Lexter [28], Phemister [37] and Seen [42], during the late 19th and early 20th centuries. These substantive scientific contributions have made bone grafting techniques common and relatively effective clinical procedures.

There are three biologic processes that impact the success or failure of bone graft: osteogenesis, osteoconduction, and osteoinduction [5].

Osteogenesis refers to the process whereby bone forms directly from living cells, such as the stem cells within autogenous bone. Osteoconduction describes the process in which bone grows into and along the surface of a biocompatible structure when placed in direct apposition to host bone through the process of intramembranous bone formation. The ability to osteoconduct is a passive characteristic of bone that allows it to act as platform on which vascular invasion, resorption, and new bone formation can occur [16]. Osteoinduction is an endochondral bone growth stimulated by specific growth factors (morphogens and/or mitogens) on pluripotential cells, such as mesenchymal stromal or stem cells. In particular, bone morphogenic protein (BMP), identified through the seminal work of Urist and colleagues [48], has demonstrated the capacity for inducing the differentiation of host perivascular mesenchymal cells into cartilage and bone [26].

In varying degrees, bone grafting source materials and techniques use these mechanisms of bioincorporation. Thus, the ideal bone graft should be capable of these processes and also be free of immunologic antigens and microbial pathogens. There are a variety of bone grafts to choose from, each presenting a unique set of advantages and disadvantages. Autograft, or autogenous bone, represents the bone graft source used in the majority of clinical applications.

Autografts, because they are harvested from host bone stock from one body site for transfer to another location in the same individual, offer the maximum biologic potential and histocompatibility. Immunologic considerations and disease transmission are obviated through the use of autogenous bone.

The possibilities of meeting the needs of size, shape, and quantity of bone for any given procedure, however, are limited in autografting. The potential for morbidity by harvesting autologous iliac bone graft is ever present [52], and can be caused by nerve injuries [4, 7, 8, 9], vascular injuries [14, 27], hernia through the iliac bone donor site [17, 29], bowel obstructions [6], and other noteworthy drawbacks. Operating room time is extended, as is the period under which the patient must remain under anesthesia. Any complications arising from these events, especially if compounded by the sequelae of donor site morbidity, may also increase the duration of hospitalization. Moreover, such a procedure often renders the bone donor site unacceptable for a subsequent operation.

Despite these disadvantages, what makes the autograft the gold standard for bone grafting is that it fulfils the three requirements necessary for bioincorporation: it is osteogenic, osteoconductive, and osteoinductive.

Allografts, usually obtained from cadaveric sources or incidental to operative procedures, offer satisfactory biologic potential and eliminate the chance of donor site morbidity. For same species to species transfer, allografts provide an abundant supply of bone tissue, but the use of allografts for spinal fusion has proven disappointing, especially for onlay intertransverse bone grafts [19, 21, 45]. Moreover, the use of allografts poses biohazards arising from their potential to act as conduits for disease transmission from donor to recipient and the triggering of immunologic reactions. Thus, strict adherence to bone banking methodology and sterilization procedures are essential to proper handling of allografts [44].

Xenograft, or cross-species bone tissue, although in abundant supply, has been found to be a less reliable graft material than autogenous and allogeneic bone. The emergence of such concerns as major histocompatibility difference leading to immune response provocation, the incompatibility of other species' anatomies with human anatomic parts, lessened biological activity, and the need for rigorous, meticulous processing and sterilization of bone derived from non-human species have largely reduced the opportunities for effective orthopaedic reconstructive use of xenograft bone.

The endeavor to transcend the numerous drawbacks associated with natural sources of bone tissue has given rise to the development and manufacture of bone substitutes in various osteoinductive and osteoconductive forms [5, 16].

Osteoconductive agents are: tricalcium phosphate ceramics (TCP), hydroxyapatites(Ht), coral-derived biomaterials, mineralized collagen matrix (Healos), some osteoactive polymers and calcium sulphate (plaster of Paris; POP). Materials with osteoinductive properties are: demineralized bone matrix, bovine osteogenic factors and bone derivatives such as BMP and osteogenin. Osteogenesis refers to the process whereby bone forms directly from living cells, such as the stem cells within autogenous bone.

For some applications, such as intervertebral fusions, biologically compatible materials are most suitable when they provide geometric spaces that invite the ingrowth and osteogenic differentiation of primitive mesenchymal cells. "Industry" has exploited this knowledge by providing porous calcium phosphate ceramics [10, 18, 25] and the orthopedic implants with porous metallic coating, which are now widely employed in hip and knee replacement surgeries. Suitable "biological space" was also found in coelenterate coral skeletons. Once it was discovered how to chemically convert $CaCO_3$ to bone-like hydroxyapatite, this material was marketed as bone ingrowth system under a number of trademarks (e.g., Interpore 200/400; proOsteon Implant 500). There is now a sizeable outcome literature reporting successful use of replamineform coral implants. (i.e., bony union) in the canine mandible [23], and tibial plateau [23], in a rabbit tibia [43, 46], as well as in various human long bones [24]. However, osseous integration, which is usually promoted by hydroxyapatite coating, failed to occur on artificial intervertebral disc in dogs. To date, there is a single report that plate-stabilized blocks

(0.5 cm) of coralline material produce new bone within cervical disc spaces [49].

BMP has been demonstrated to improve the spinal fusion rate [47], but its expense and limited availability are not likely to encourage its widespread use in the near future. An inexpensive, readily available bone grafting material that has a high fusion success rate would be greatly welcomed. POP may prove to be such a material since, in non-vertebral settings, it is well tolerated by human tissue. POP-filled defects in bone are gradually vascularized and replaced by bone tissue derived from the host [11, 30, 33, 34, 35, 36].

The goal of this paper is:

1. To determine whether POP implants in resected vertebral bone spaces in adult sheep are as effective as autologous bone, allogeneic bone, demineralized bone and Interpore-500 in achieving lumbar intervertebral fusions, and
2. To review the pertinent literature on POP as bone substitute

Table 1 Graft materials used to fill tubular titanium mesh implants

Osteoconductive grafts	Osteoinductive graft
1. Autogenous iliac crest cancellous bone	Demineralized bone
2. Frozen allogeneic cancellous iliac crest	
3. Coralline hydroxyapatite (pro-Osteon 500)	
4. Plaster of Paris	
5. 1:1 autogenous iliac crest bone with:	
a) Frozen allogeneic bone	
b) Replamineform coral	
c) Plaster of Paris	

Materials and methods

Animals

Fifteen adult female sheep (30–40 kg body wt) were purchased through the UTMB Animal Resources Center. They were penned in individual cages with free access to food and tap of water. The full-time animal care staff monitored the health of the animals pre- and postoperatively, and the animals were inspected three times a day, including weekends. All experimental procedures were carried out with the approval of the Institutional Animal Use and Care Committee (ACUC Protocol # 94–07–036)

Surgical procedures

The animals were intubated, and anesthetized by deep halothane inhalation (2–4%). The skin was sheared and shaved over the region of their lumbar vertebrae, and was sterilized with a betadine scrub. Using aseptic conditions, the intervertebral discs between L1-L2, L3-L4, and L5-L6 were excised by sharp dissection and the use of a pituitary forceps, and the cartilaginous and bony end plates were cut away to expose the subchondral bone. Each space was then implanted with a 1.0×1.5-cm-long tubular titanium cage (DePuy Motech, Warsaw, Ind.), which had been filled with one of a variety of osteoconductive or osteoinductive demineralized bone substrates (Table 1, Fig. 1), or left empty as a control implant. The autogenous iliac crest implants containing bone and marrow were morselized (1–2 mm) prior to loading and implantation. The osteoinductive substrate was donated by Osteotech Inc., whose technical staff prepared the material from powdered/sieved (size range=100–500 mm) allogeneic sheep cortical bone according to the general methods reported by the Edwards' group [12]. POP was obtained from the Galveston Shriners Burne Hospital's orthotic laboratory, and implanted as 2- to 4-mm^3 pellets. The implant of a commercially available porous apatitic coralline material (Pro-Osteon 500, Orthopaedics Inc., Irvine, Calif.) was coarsely granular. Implant usage was randomized by implanting two grafts of each type at the three different levels (n=6/group) (Table 2). The subcutaneous muscles were reapproximated and sutured with 2–0 chromic sutures. The skin incisions were closed with surgical staples.

Immediately after surgery, the animals were removed to the ovine intensive care unit, where they were closely monitored for

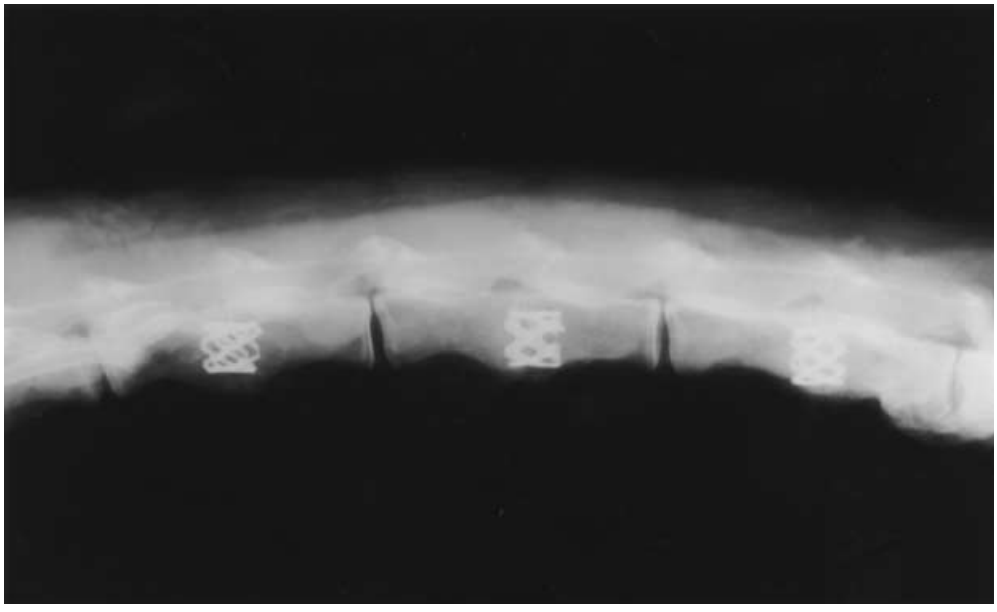


Fig. 1 Roentgenograph showing the positioning of titanium cages within excavated disc spaces in the lumbar spine of a sheep 4 months postoperatively. The interbody fusion masses represent the following graft types. *Top*: autogenous iliac crest bone/marrow; *middle*: demineralized allogeneic bone (DBM); *bottom*: 1:1 autograft:DBM. The roentgenograph is showing the interbody fusion masses within and around the titanium cages

Table 2 Example of distribution of graft types at three lumbar spinal levels in sheep (n=7/group)

Sheep no.	Disc space level	Graft material	Post-surgical radiology	Postop. time to sacrifice
1	L1–2	Autogenous iliac crest	48 h & 1,2,3,4 months	4 months
	L3–4	1:1 autogenous iliac crest and replamineform coral		
	L5–6	Replamineform coral		
2	L1–2	Autogenous iliac crest.	48 h & 1,2,3,4 months	4 months
	L3–4	1:1 autogenous iliac crest and plaster of Paris		
	L5–6	Plaster of Paris		

pain and discomfort, food and water consumption, and urinary output. Pain was managed by the subcutaneous administration of Buprenex (0.15 mg). All animals exhibited an unremarkable postoperative course, and were able to stand independently within 12–24 h. The animals were sacrificed 4 months postoperatively by an intravenous injection of Beuthenasia (1.0 ml/10lb body wt). At autopsy, the thoracolumbar vertebral columns were stripped of soft tissues and their posterior bony elements (facet joints), and frozen in saline for biomechanical and histomorphometric studies.

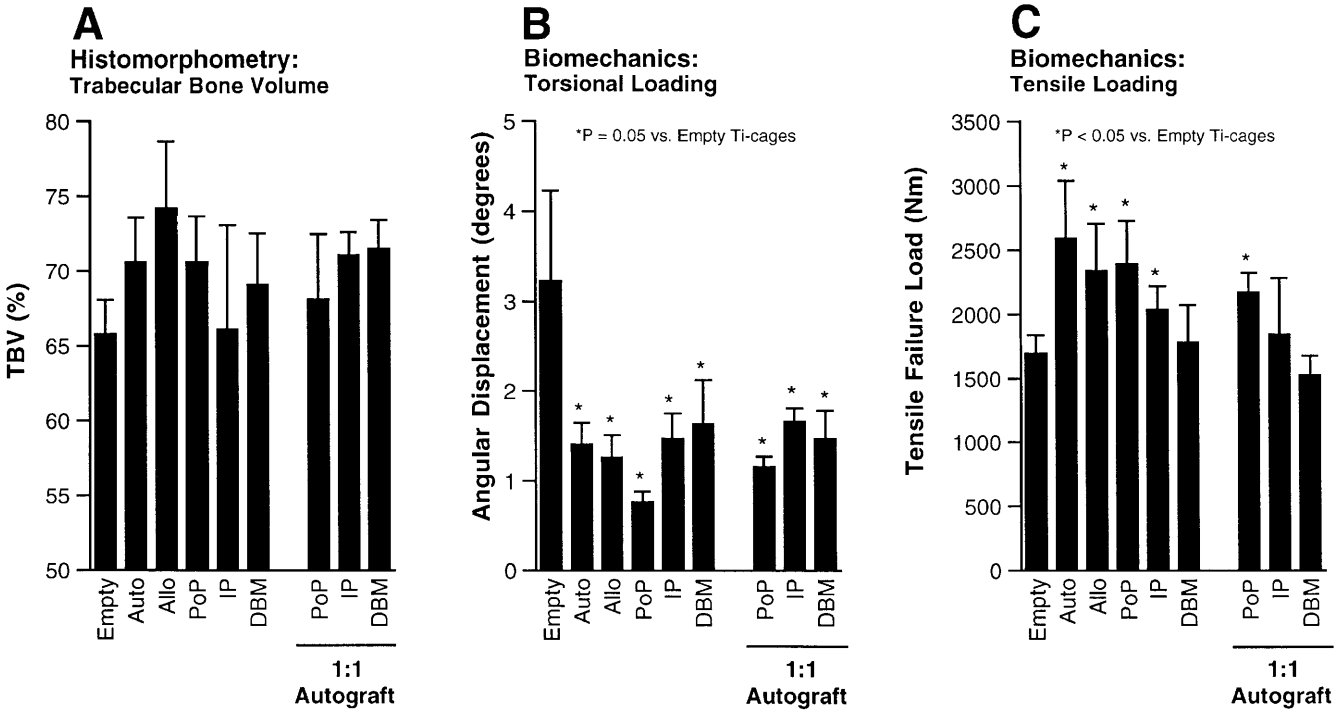
Fig. 2A–C Graphs showing the quantitative histomorphometric and biomechanical evaluations of the bone formed under the influence of osteoconductive and osteoinductive substrates implanted within excavated lumbar spine spaces. **A** Histomorphometry, **B** biomechanics – angular displacements between –2.5 and +2.5 N m loads, **C** biomechanics – tensile failure load. Implants of empty titanium cages served as the control group. Data represented by bars marked with an asterisk (*) were statistically different from the empty control data at the $P<0.05$ level of significance (*Auto* autograft, *Allo* frozen allografts, *PoP* plaster of Paris, *IP* replamineform coralline substrate, *BDM* demineralized allogeneic sheep bone)

Biomechanical investigations

All testing was carried out using an MTS –858 Mini-Bionix machine (MTS Inc., Minneapolis, Minn.). Vertebrae were transected at their midlengths, so that the ends of individual segments, which included a single interbody graft, were mounted in methylmethacrylate. The stability of these segments was tested in two modes:

1. In torsional loading through a range of 5 N m (–2.5 to +2.5 N m) to establish rotational stability, and
2. In tensile loading to measure the tensile load to failure (N)

Longitudinal sections showed that the ±2.5 N m of torque applied to the normal vertebrae was insufficient to break trabecular bone structures (vide infra). Following the biomechanical extension test (which produced titanium-free bony cores), the tissues were recovered for histomorphometric investigations. In the protocol for (1), the loading rate was 0.1 Hz, and each sample was subjected to two complete cycles. In (2), the tensile loading was applied from a 0.05 N preload at a rate of 0.5 mm/s.



Histomorphometric investigations

Interest focused on the relative volumes of bone that had formed within the titanium cages. The intact cores of bone with attached vertebrae were fixed in 95% ethyl alcohol, defatted in acetone, and embedded in methylmethacrylate, and serial longitudinal sections (100 μm thick) were obtained at midlength level using a low-speed Isomet saw (Buehler) equipped with a diamond blade. The sections were microradiographed on fine-grain 649–0 spectroscopic film (10 kV, 20 mA, 10 min). A point-counting microscopical technique with computer-driven software (Optimas Corp., Bothell, Wash.) was employed to quantitate the total area of trabecular bone formed within each titanium cage, and the data were expressed in terms of percent trabecular bone volume.

Statistics

The experiments were designed with the recognition that there might be significant positional effects of grafts at the different spine levels. Nevertheless, our protocols produced too few numbers of grafts for any one to detect such effects. The data were expressed as the mean±standard error of the mean (SEM). The differences between the means were analyzed by Student's *t*-test when the variances were equal (ANOVA), or by a nonparametric two-tailed *t*-test, *F*-test, and Wilcoxon rank-order statistic when the variances were unequal. Differences between means at the 5% confidence level ($P<0.05$) were considered to be statistically significant. The statistical power at $\alpha=0.05$ ranged from 0.8 to 1.0 for the variables that showed statistical significance.

Results

At the time of sacrifice, 4 months postoperatively, host-derived trabecular bone had invested each of the control and experimental interbody cages (Fig. 1). Histomorphometry indicated that the different grafts and combinations of tissue types had produced volumes of new bone that were neither significantly different interalia, nor different from the outcome of the empty control implants (Fig. 2 A). This indicated that the postoperative recovery period was sufficiently long to model and remodel the original graft matrices. All bone present appeared microradiographically to be of uniform and equal density. Biomechanically, however, the behavior of the control fusion masses was inferior to that of the fusion masses formed under the influence of osteoconductive bony and apatitic substrates. An applied torque of ±2.5 N m (from –2.5 to +2.5 N m), which was insufficient to break the bony trabeculae, permitted a 1°–2° displacement in the experimental groups (Fig. 2B), versus 3°–4° displacement in the trabecular masses formed around the control cages. The POP grafts permitted, quantitatively, at least, the smallest angular displacement. The "pull-out" tensile test also affirmed that POP and most of the other osteoconductive experimental graft types, alone or in combination with autologous bone, performed optimally (Fig. 2C), and that their fusion masses were biomechanically superior to those formed around the control cages. The tensile failure load of the sheep demineralized osteoinductive bone was only equal to that of the control titanium cages that were implanted empty.

Discussion

This study was designed to determine whether POP could be used to promote interbody lumbar spinal fusions as effectively as autogenous iliac crest bone or a variety of other bone graft preparations. Therefore, comparisons were made to autografts, frozen allogeneic bone, demineralized sheep bone preparation (DBM), replamineform coralline skeleton (Interpore), and to admixtures of POP, DBM and Interpore. These materials were loaded into short (1.0× 1.5 cm) titanium mesh cages, inserted into lumbar disc spaces, and recovered for microradiographic-histomorphometric and biomechanical analysis after 4 months. The histomorphometric results suggested that the different graft types were equally effective at producing bone. The absence of obvious signs of aberrant bone formation (e.g., irregularities in trabecular thickness) indicated that the distributions of viable and dead bone were probably similar in each experimental group. Microradiography per se was incapable of making such distinctions. Moreover, biomechanical tests indicated that in terms of measures of torsional strain (Fig. 2B), tensile failure (Fig. 2C), and volume of bone formed within the titanium cages, the effects of POP and autogenous bone were as indistinguishable from each other as POP was to Interpore and 1:1 admixtures of those substrates with autogenous bone. Elkins and Jones also noted no difference in the degree of bone healing between autogenous cancellous bone, POP and a composite of POP and autogenous cancellous bone [13]. Despite contrary expectations, the osteoinductive demineralized sheep bone preparations proved the least effective of the different substrates in achieving a solid interbody fusion, even though tissue from other species prepared in an identical fashion [39] has proved to be osteoinductive [22, 40, 51]. The addition of autogenous bone did little to improve DBM performance. The advanced age of the donor animals could have been a factor in its poor performance, since production of bone morphogenetic proteins declines with increasing maturity [3]. Yet, it may be that mature sheep are poor BMP responders [15, 41]. This should be taken into consideration with further investigation.

The mechanism(s) responsible for the new bone formation that enveloped the titanium-carrier mesh is likely to involve vascular ingrowth from the marrow of the vertebral bodies, with the intercession of the vertebral periosteum and psoas muscle pericytes (osteoprogenitor cells). The probable involvement of these juxtavascular mesenchymal cells in psoas muscle was observed in sheep implanted with long (44×15-mm) tubular titanium cages to bridge an L4 osteotomy, where the chamber fully ossified within 6 months [20]. Because the most posterior annular tissue had not been completely removed, it is unlikely that

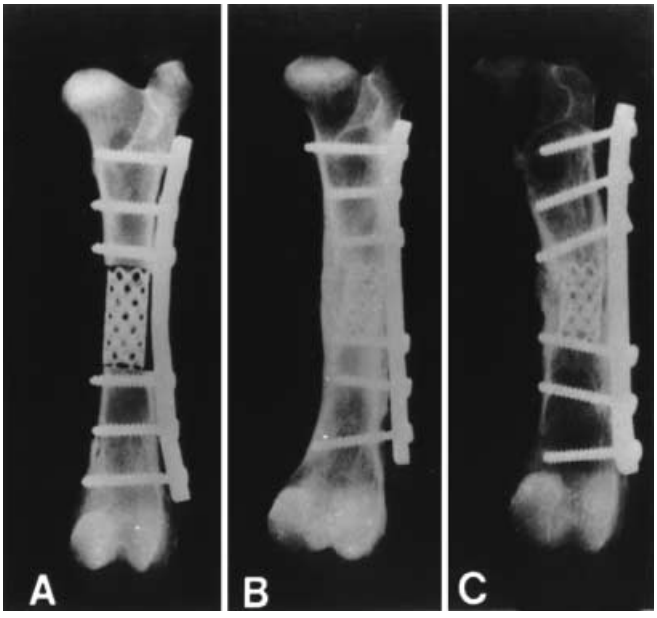


Fig. 3 Roentgenographs showing postoperative appearances of a femoral midshaft titanium cage implant in a sheep: immediately after surgery (**A**), 6 months after iliac crest autograft procedure (**B**), and 6 months after POP implant (**C**). All graft sites were stabilized by lateral eight-hole compression plate (with permission from Lippincott Williams & Wilkins)

the formation of the fusion masses was mediated in part by osteogenic potential of the dura. In addition, an important finding in this study was that the tissue formed within and around the titanium mesh implanted with POP and autogenous bone marrow had equal biomechanical competence in the bending and torsional modes.

In a previous publication we have reported that POP had an osteoconductivity equal to that of autogenous iliac crest marrow/bone (Fig. 3, Fig. 4) [20]. Our study corroborated the findings of Peltier and co-workers [35, 36], which showed that the most important property of POP as a "filler" was its apparent natural rate of absorption – one that was equal to the rate at which new bone grew into the defect. Peltier's findings were further reinforced by a previous observation by the present authors that equal volumes of bone were produced by POP and autogenous bone marrow preparations, and that the products were of equal biomechanical competence in bending and torsion testing modes [20].

Allergy to POP, although rare and related to minor additives, and inflammatory reactions should be considered when assessing the risk-benefit of using calcium sulphate as bone replacement material [38]. In a series of 15 implantations of calcium sulphate pellets (Osteoset, Wright Medical Technology) used for bone reconstruction after resection of bone tumors, three cases of inflammatory reactions were noted [38].

In one case, an allergic reaction provoked serious drainage and necessitated graft removal. In another case, inflammation resolved 2 months following implantation, whereas the third case was complicated by wound breakdown. However, other investigators have noted that POP is innocuous in terms of producing a local soft tissue chemical or pyogenic inflammatory reaction [20, 13, 35].

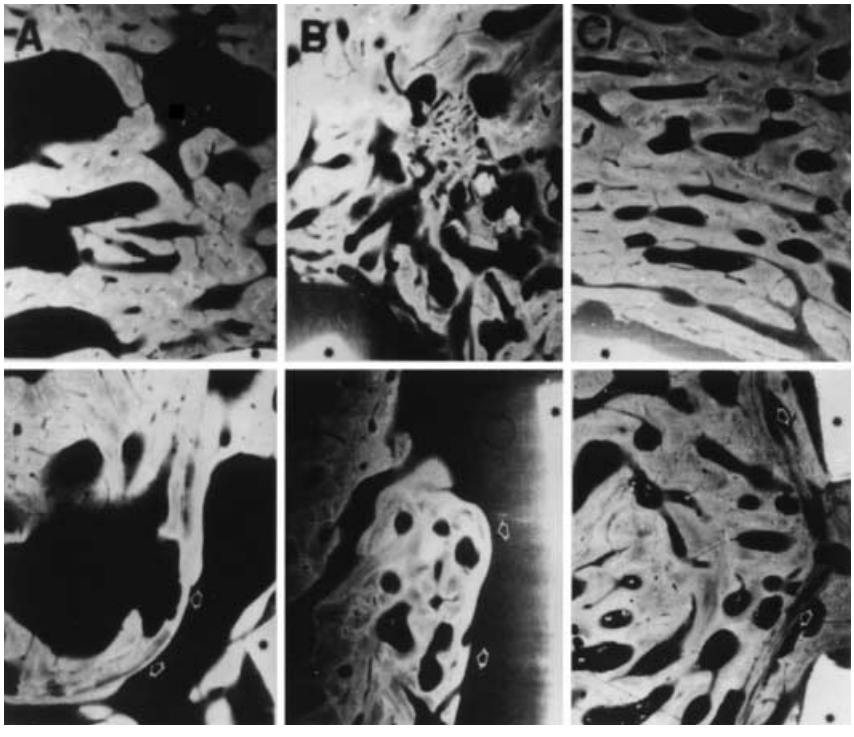


Fig. 4A–C Microradiographs showing the relative amount and structure of the bone formed external to (*top*) and within (*bottom*) the titanium cage midshaft femoral implants in sheep 6 months after surgery. **A** control/empty, **B** autogenous bone/marrow, **C** POP (with permission from Lippincott Williams and Wilkins)

In a prospective clinical study of 50 patients using calcium sulphate pellets (Osteoset), no graft complication was encountered [50].

A recent clinical study of 50 patients showed that POP (an osteoconductive material) is very effective when used as a vehicle for a bioassayed demineralized bone matrix (an osteoinductive material), comparable to grafting with autograft [50]. These findings suggest that POP may be considered as a suitable vehicle through which osteoinductive material may express optimal osteoactivity.

POP may also be considered as an effective carrier for the local delivery of antibiotics. The elution of POP is 17% at 24 h; at 3 weeks trace amounts are still detected. This profile compares favorably to the more conventional carrier, polymethylmethacrylate, which releases 7% of its load by 24 h, with trace amounts detected at 14 days. Because POP remains effective for approximately 3 weeks, it offers a suitable means for long-term coverage of established osteomyelitis [31]. For acute contaminated open fractures, where brief antibiotic coverage is required, bone graft or demineralized bone matrix (DBM) may be used for local delivery, because they elute 70% and 45% of their antibiotic load by 24 h, respectively, and negligible amounts are detectable at 1 week [31].

We have not tested the effects of POP on common bone formation and resorption markers (e.g., alkaline phosphatase, osteocalcin, osteopontin). We are currently using histomorphometric studies to compare the rates of bone formation and resorption between normal bone and POP. In future studies, we intend to investigate the effects of POP in the proximity of neural elements such as dura and nerve roots.

In conclusion, the biomechanical histomorphometric outcomes of interpositional grafts of POP were equal to those of autogenous bone marrow grafts.

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