The Assay of Bone Reaction after Implantation of Calcium Sulfate and A Composite of Calcium Sulfate and Calcium Phosphate

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Abstract

The in vivo implantation of calcium sulfate and a composite of calcium sulfate and calcium phosphate of the proximal epiphysis of tibia of the rabbit was investigated to evaluate biocompatibility, bioabsorbability and biodegradability. The materials were in situ for 6, 12 and 24 weeks in 3 different groups of rabbits in all 6 cases. Light microscopy reveals calcium sulfate in bone marrow is completely resorbed and replaced by connective tissue and fatty tissue. Significant osteogenesis is noted once calcium sulfate contacts with periosteum and endosteum. We do not recommend use of calcium sulfate as filler of bone defect because new bone formation is not ideal due to fast absorption of implant. A composite of calcium sulfate and calcium phosphate is slowly resorbed. The absorbed calcium sulfate will be used as materials of bone matrix. It will cause a porous effect in composite. The newly formed bone integrates into the implant along with the pore and contacts directly with crystals of calcium phosphate. Osteoblasts are in direct contact with implanted granules of calcium phosphate. There is no evidence of acute or chronic inflammation. Therefore a composite of calcium sulfate and calcium phosphate is considered a good choice of bone defect filler.

***Keywords*:** Calcium sulfate, Calcium phosphate, Bone graft

Introduction

Surgeons often transplant bone grafts to treat delayed union, nonunion of an old fracture and to fill the defect after enucleation of bone tumor or saucerization for osteomyelitis or severe trauma for improving bone healing. Although autogeneous bone grafts are always the most popular procedure, autogeneous bone grafts may cause donor site morbidity, for example: pain, fracture, infection and the risk of anesthesia due to longer operative time. Sometimes we cannot take enough cancellous bone for filling the large defect. Although allograft can supply enough cancellous bone for operation, patient must be exposed to the risk of the failure of each screening technique of AIDS or the other immunological disease [1] or undetected infectious disease. Heterograft of bovine also exposes the risk of bovine spongioform encephalopathy or mad-cow disease [2]. Therefore new materials as a substitute for bone grafts are studied in order to avoid the above complications. The purpose of this study was to compare the tissue compatibility, resorbability and osteogenesis between calcium sulfate and a composite of calcium sulfate and calcium phosphate.

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Materials and Methods

Materials

A total of 6 adult New Zealand rabbits (3 of which were female) with weights ranging from 2.3 to 3.1 kg (average 2.8 kg) were separated into 3 groups of 2 each. We studied two kinds of setting cylinder implants (Fig 1). They are made of calcium sulfate or a composite of calcium sulfate and calcium phosphate whose diameter is 6.5 mm and 5mm in height. What is calcium sulfate? Gypsum is a common mineral consisting of calcium sulfate dehydrate ($CaSO_4$-$2H_2O$). Plaster of Paris is the hemihydrate of $CaSO_4$-$2H_2O$. The hemihydrate of $CaSO_4$ is manufactured by heating gypsum ($CaSO_4$-$2H_2O$) in such a way that it loses three quarters of its water of crystallization:

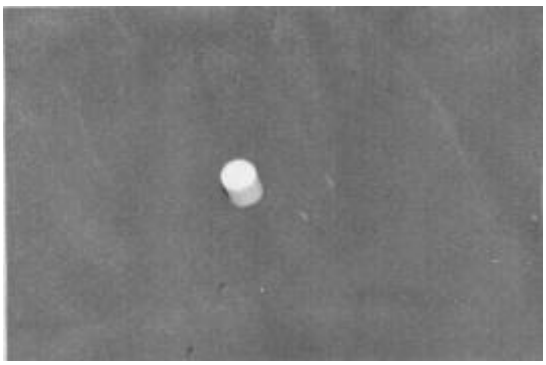

Figure 1. This is a cylindrical implant with 6.5mm in diameter and 5mm in height.

Figure 2. A cylindrical implant was impacted into the medial aspect of the proximal epiphysis of left tibia during operation..

$$CaSO_4\text{-}2H_2O \rightarrow CaSO_4\text{-}\frac{1}{2}H_2O + 1\frac{1}{2}H_2O$$

Once hemihydrate of $CaSO_4$ is mixed with water, it solidifies:

$$CaSO_4\text{-}\frac{1}{2}H_2O + 1\frac{1}{2}H_2O \rightarrow CaSO_4\text{-}2H_2O$$

This reaction is setting. In this study the implant is the setting form of calcium sulfate. The other implant is a composite of calcium sulfate and calcium phosphate.

Surgical procedure

The rabbit was anesthetized with ketamine 50mg/kg intramuscular injection at first and kept with sodium pentobarbital (concentration 10mg/ml) intravenously. Once anesthesia was obtained (about 5 to 10 minutes), the animal was placed in the supine position and the extremities were held with string. The hair over the medial aspect of both knees was shaved. Skin was aseptic with betadine. A longitudinal incision about 3 cm in length was performed over medial aspect of left knee and exposed the medial epiphysis of proximal tibia. The muscle and connective tissue were dissected. Periosteum was incised. We drilled a hole, 1 cm to 1.5 cm apart from the medial condyle of tibia with a hand drill. The size of the hole was 6 mm in diameter and 5 mm in depth. A cylindrical implant of calcium sulfate was impacted into the hole (Fig 2). And then the implant was covered with incised periosteum. We drilled another hole the same size as the left tibia over the medial aspect of the distal epiphysis of the left femur for the control group. The incision wound was sutured using 4-0 nylon. The right tibia received the same operative procedure but it was impacted with an implant of a composite of calcium sulfate and calcium phosphate. We gave one dose of cephalothin sodium (Keflin) via venous for preventing infection after operation.

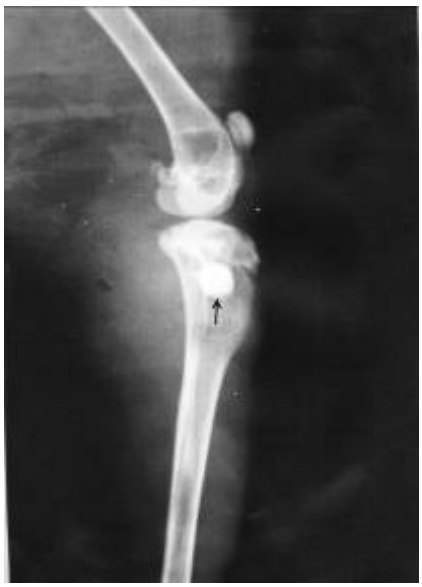

Figure 3. A lateral view of X-ray film of left knee after grafting implant

Postoperative care and follow-up

We took X-Ray films of anteroposterior and lateral views of both knees before the animal had recovered from anesthesia (Fig 3). The rabbit was allowed to recover from anesthesia, and was returned to its cage, separately. It was fed a special diet for rabbit until sacrifice at 6, 12, and 24 weeks. We took repeated X-Ray films of anteroposterior and lateral views of both knees at 6, 12, and 24 weeks.

Histologic Processing

The animals were killed with ketamine via intramuscular injection (50mg/kg) and 15% potassium chloride 5c.c. intravenous injection. After the animals were sacrificed, both knees 4 cm apart from the joint were dissected from the soft tissue. We checked the implanted position by gross inspection. Specimens were sawed into several pieces with thickness of 2mm through the implant. Specimens were sunk in a 10% neutral buffered formalin solution for 24 hours and then moved to Formic acid-Sodium citrate solution until fully decalcified. Specimens were rinsed in running tap water for 5 hours to remove excess acid from the tissue. Specimens were dehydrated in increasing percentages of ethyl alcohol (80 to 100 %). Specimens were impregnated in melted paraffin wax. The embedded samples were sectioned with a rotatory microtome in 5-8 μm slices. Sections were mounted on glass slides, stained with hematoxylin-eosin, and washed with water. Sections were rehydrated and sealed with cover slide. The other specimens were dehydrated in increasing percentages of ethyl alcohol (70 to 100 %) and embedded in polyester resin to obtain undecalcified specimens. The blocks were sawed obtaining 1mm thick sections, then ground with abrasive paper and flannels. The specimens were fixed on acrylic slides with cyanocrylate adhesive. All specimens were observed histomorphologically.

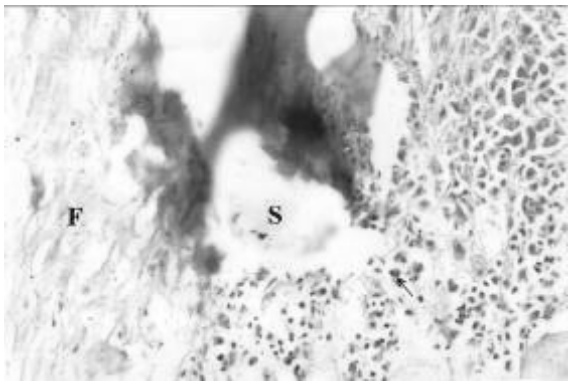

Figure 4. A decalcified section of being grafted calcium sulfate at 6 weeks. Calcium sulfate was replaced by a large amount of fibrous tissue (F). Unabsorbed granules (S) of calcium sulfate showed in the middle of the picture. Polymorphonuclear cells (arrow) surrounded the implant. There is no evidence of foreign body giant cell formation. (hematoxylin-eosin,original magnification × 400)

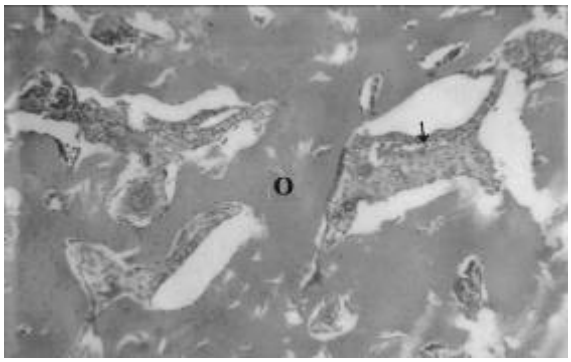

Figure 5. A decalcified section of being grafted calcium sulfate and calcium phosphate at 6 weeks. Newly woven vital bone with uncalcified osteoid (O) lining with osteoblasts and neonatal vessels (arrow) were noted. (hematoxylin-eosin,original magnification × 100)

Results

All but one rabbit tolerated the surgical procedures well. One rabbit died at the end of surgery due to anesthesia complications. There was no evidence of infection or ulceration of surgical wounds throughout the study. The experiment stage was divided to three period, including 6, 12, 24 weeks.

Six weeks

Implantation of calcium sulfate

X-rays films findings: Most of calcium sulfate was absorbed and left a radiolucent shadow.

Gross inspection of implanted site：We noted that there was good contact between implant and peripheral bone tissue but decreasing in size. There was no evidence of inflammation.

Morphology: A large amount of dense fibrous tissue surrounded the scanty unabsorbed granules of calcium sulfate. Fibroblasts appeared in fibrous tissue. Many polymorphonuclear cells were present neighbored to fibrous tissue but there was no giant cell (Fig 4).

Undecalcified specimens: Most of the crystal of calcium sulfate was destroyed and absorbed.

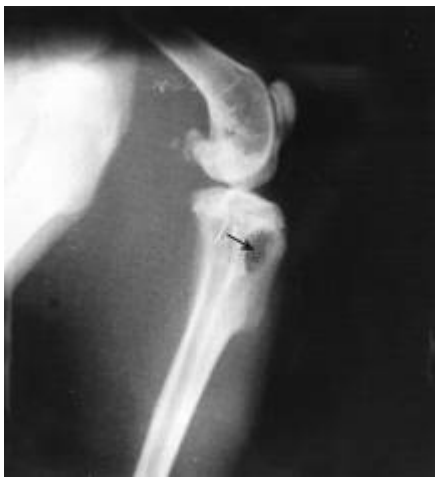

Figure 6. A lateral view of X-ray film of left knee after being grafted calcium sulfate for 12 weeks. All of calcium sulfate has been absorbed and left a radiolucent shadow. There was a little of radiopaque shadow (arrow) caused by osteoid and dense fibrous tissue.

Implantation of a composite of calcium sulfate and calcium phosphate

X-rays films findings: Scanty implant was absorbed and left an unremarkable radiolucent shadow.

Gross inspection of implanted site: We noted that there was a good contact between the implant and peripheral bone with good demarcation. There was no evidence of inflammation.

Morphology: Scanty fibrous tissue surrounded the implant. Many polymorphonuclear cells were present neighbored to fibrous tissue but there was no giant cell. Newly woven vital bone with uncalcified osteoid lining with osteoblasts and neonatal vessels were noted neighbored to the cortex (Fig 5).

Undecalcified specimens: The center of implant of the composite calcium sulfate and calcium phosphate is very impacted but the peripheral part was destroyed into many granules.

Twelve weeks

Implantation of calcium sulfate

X-rays films findings: All of calcium sulfate had been absorbed and left a radiolucent shadow. A little linear radiopaque shadow caused by osteoid and compact connective tissue was noted (Fig 6).

Gross inspection of implanted site: Most of the implant had been absorbed except scanty central location of calcium sulfate. Bony healing around the residual implant was good.

Morphology: Part of the fibrous tissue transformed into osteoid and new bone formation. We can find the osteoblasts and osteoclasts in lacuna on the edge of new bone. The inlet of implant was sealed with thin new bone. There was significant osteogenesis and new trabecula of the cortex neighbored to the implant. New trabecula extended into the bone marrow. Osteocytes, neovessels and scanty unabsorbed granules of calcium sulfate were found in new bone.

Undecalcified specimens: There was new formation of lamina. Trabecula which contained rich vessels grew into bone marrow (Fig 7).

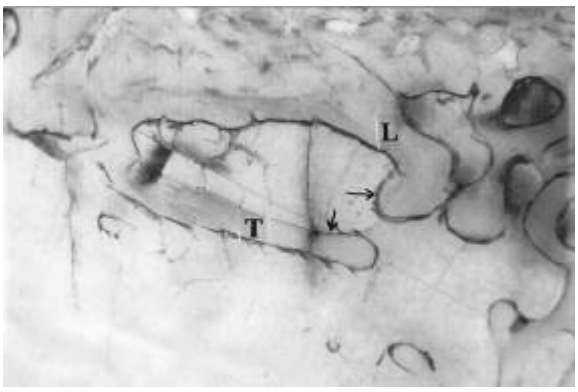

Figure 7. A undecalcified specimen of being grafted calcium sulfate at 6 weeks. There was new bone formation of lamila (L). Trabecula (T) which contained rich vessels grew into bone marrow (arrow). (magnification × 40)

Figure 8. A piece of cross section of being grafted calcium sulfate at 24 weeks. All of calcium sulfate has been replaced by connective tissue and fat (S).

Implantation of a composite of calcium sulfate and calcium phosphate

X-rays films findings: Partial implant has been absorbed and left a remarkably radiolucent shadow.

Gross inspection of implanted site: Partial implant was absorbed and decreased in size. There was good contact between implant and peripheral bone. There was no evidence of inflammation.

Morphology: Fibrous tissue surrounding the implant significantly decreased. Mineralization of new bone was remarkable. Osteoblasts lined on the edge of new bone.

Undecalcified specimens: The volume of the grafted implant was significantly decreased. The space of each granule of calcium phosphate was increased.

Twenty-four weeks

Implantation of calcium sulfate

X-rays films findings: All of the calcium sulfate had been absorbed and left a radiolucent shadow, but the area of radiolucent shadow was significantly decreased.

Gross inspection of implanted site: Site of grafted implant could not be found except mark.

Morphology: A great deal of new bone formation of the cortex neighbored to the inlet of grafted implant was noted. The space between the lamina of new bone was filled with a normal

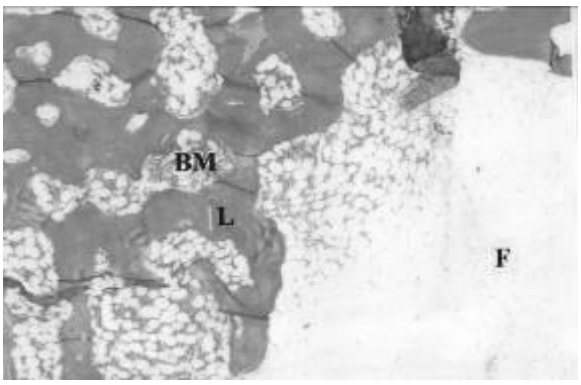

Figure 9. A decalcified section of being grafted calcium sulfate at 24 weeks. There was a great deal of network new bone formation (L) of the cortex neighbored to the inlet of grafted implant. The space between lamina of new bone is filled with normal structure of bone marrow (BM). Fatty bone marrow and connective tissue (F) completely replaced of the grafted calcium sulfate.
(hematoxylin-eosin, original magnification × 100)

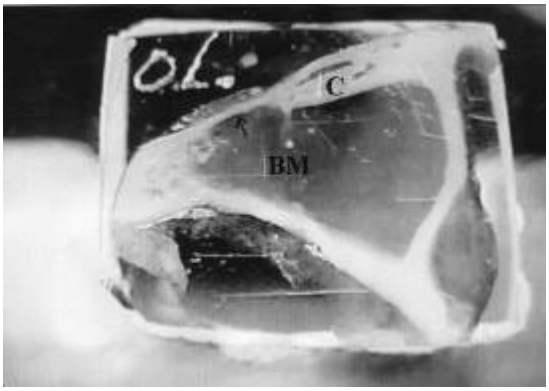

Figure 10. A undecalcified specimen of being grafted calcium sulfate at 24 weeks. Inlet (arrow) of grafted implant was completely closed by new bone formation. Significant osteogenesis (C) of lamina of new bone neighbored to inlet of grafted implant was noted. There was scanty unabsorbed calcium sulfate in bone marrow (BM). (magnification × 40)

structure of bone marrow and fatty tissue. Little of the unabsorbed granules of calcium sulfate were buried in the lamina of new bone. Fatty bone marrow completely replaced the grafted calcium sulfate (Fig 8, 9).

Undecalcified specimens: Inlet of grafted implant was completely closed by new bone formation. Significant osteogenesis of lamina of new bone neighbored to the inlet of grafted implant was noted. Little of the unabsorbed granules of calcium sulfate were buried in the lamina of new bone (Fig 10).

Implantation of a composite of calcium sulfate and calcium phosphate

X-rays films findings: The area of radiolucent shadow due to resorption of grafted implant was more remarkable. The radiopaque shadow due to residual grafted implant was fainter (Fig 11).

Gross inspection of implanted site: Most of the grafted implant was absorbed and had left the central part.

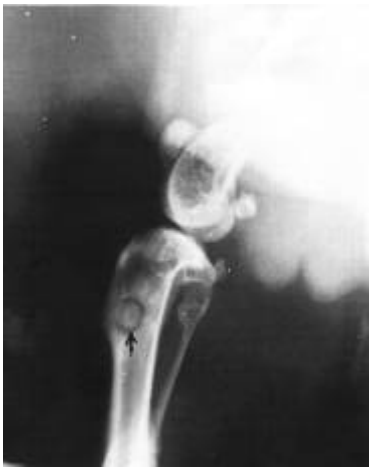

Figure 11. A lateral view of X-ray film of right knee after being grafted calcium sulfate and calcium phosphate for 24 weeks. Peripheral part of implant has been absorbed and left a more area of radiolucent shadow (arrow). The radiopaqueshadow due to residueal grafted implant is more faint.

Figure 12. A piece of cross section of being grafted a composite of calcium sulfate and calcium phosphate at 24 weeks. The central part of implant has burst (P).

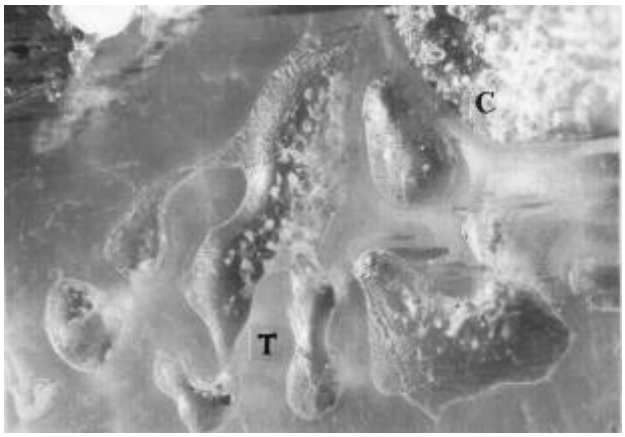

Figure 13. A undecalcified specimen of being grafted calcium sulfate and calcium phosphate at 24 weeks. A little of unabsorbed granules of calcium phosphate (C) was noted. New lamellar trabecula (T) grew into grafted implant and contacted directly with granular of calcium phosphate. (magnification × 40)

Morphology: The network new bone formation containing osteocytes and lamellar structure was noted. The space between lamina was filled with normal bone marrow. Undecalcified specimens: A few unabsorbed granules of calcium phosphate was noted (Fig 12). New lamellar trabecula grew into the grafted implant and contacted directly with granules of calcium phosphate (Fig 13).

There was no osteogenesis of the cortex over the control hollow of the left distal femur. The bone marrow of the control hollow was replaced by fatty connective tissue.

Discussion

In 1892, Dreesmann [3] first reported results of filling bone voids with calcium sulfate. In 1955, Peltier and Lillo [4-7] studied calcium sulfate, and came to the following conclusions after experimental work on dogs: (1) Calcium sulfate not covered by periosteum showed few signs of absorption, regeneration, or deposition of bone. (2) All dogs in which the calcium sulfate was covered by periosteum showed complete disappearance of the calcium sulfate roentgenographically in 45 to 72 days. (3) Complete regeneration of the defects occurred in approximately three months, and (4) in conclusion, the hemihydrate of calcium sulfate alone was not osteogenic, but when it contacted with periosteum or bone, regeneration of bone was accelerated.

In 1955, Nikulin and Ljubovic [6] reported that regeneration of completely normal bone occurred earlier with calcium sulfate than with autogeneous grafts. In 1960, Bell[8] reported implants of calcium sulfate were the most rapidly absorbed, taking an average time of five to seven weeks. Autogenous bone implants were absorbed in seven weeks, homologous bone took ten weeks, and bovine heterogenous bone was not resorbed in less than 11.5 weeks. The others implants were absorbed much more slowly.

In 1887, Yamazaki [9] implanted a composite consisting of 1 mg of bone morphogenetic protein (BMP) containing mesenchymal cells to form cartilage and bone tissue which was isolated from bovine cortical bone matrix and 5 mg of plaster of Paris (PLP) into the mouse femoral muscle. Control PLP without BMP was implanted into the contralateral muscle. The experiment concluded PLP could be used as one of the clinical BMP delivery systems. Grafted implant with a composite of BMP and PLP grew into osteoid, cartilage and calcified bone but control PLP was resorbed. Shaffer and App [10] have documented clinical observations. They implanted calcium sulfate material into human periodontal defects and found that defects filled with calcium sulfate alone did not induce more bone formation than non-implanted control defects. Khalid [11] has documented his experimental results. The dissolution rate of the calcium sulfate, however, empties the osseous cavity in a shorter time than that required for bone growth to occur. This results in inadequate new bone ingrowth in the spaces of the resorbed material. The lack of complete bone healing in osseous defects filled with calcium sulfate alone was a result of the absence of a scaffold that allows the bone remodeling process to take place with gradual

physiologic timing. Therefore he thought calcium sulfate alone could not be effectively used as a kind of bone defect filler. In our experiment we found that calcium sulfate did not induce inflammatory reaction. Once calcium sulfate comes in contact with bone tissue it will promote osteogenesis. Otherwise it will be absorbed rapidly. We also thought calcium sulfate alone was not a kind of ideal bone defect filler because it was replaced by fatty tissue in bone marrow.

In recent years, scientists have been looking for a kind of ideal bone defect filler. Calcium phosphate was studied at first because it is a main content of bony minerals. In 1986, Shoichiro and Yoshito [13] have documented their experiment. A number of composites from biodegradable polymers and hydroxyapatite were studied in vivo and in vitro. They found that polylactic acid, of low molecular weight (PLAoligomer), was rapidly resorbed and replaced by newly formed bone tissue when incorporated with hydroxyapatite and this suggested that the incorporated hydroxyapatite seemed to play an active role in new bone fomation. In 1987, Donald [14] used a composite of calcium phosphate and purified fibrillar collagen to treat 77 patients. He gained satisfactory results. In 1988, Mohamed [15] grafted the nonporous hydro- xylapatite (HA) granules and blocks as an extracranial augmentation material in monkeys. They found that the HA granules were separated from each other and from the one interface by a layer of collagen fibers, and the blocks were also surrounded by a fibrous capsule. They concluded that when used as an extracranial augmentation material, the nonporous HA granules were more stable than blocks; however the blocks maintain a better contour.

In 1998, Stuart [12] used Norian SRS as a space filling internal fixation device to facilitate the geometric reconstruction, load transfer, and healing of bone with defects and/or fractures in regions of cancellous bone. Norian SRS is a combination of monocalcium phosphate, tricalcium phosphate, calcium carbonate, and a sodium phosphate solution mixed into an injectable paste. According to his experimental results, use of this material could improve fracture stability, retain anatomy during fracture healing and improve hip function, thus achieving better clinical outcomes. In vivo animal studies have shown the material's biocompatibility, and cadaveric studies have shown the biomechanical advantage of its use in hip fracture.

In 1986, J.H.S. [16] tested various substances such as blood, albumin, and collagen in animal models to bind the particles together and to make the alveolar implant easier to shape. Hanker and his colleagues [16] found that plaster of Paris gave the best results.

In 1988, Charles [17] grafted a composite of plaster of Paris and hydroxylapatite to cranial defects in cats. The composite was made into both porous and nonporous implants. His document reported that porous hydroxylapatite showed earlier (2 to 3 months) and more extensive new bone formation under gross inspection. Histological examination revealed implants were surrounded by a large amount of dense fibrous connective tissue with relatively little bone formation and neovascularity present at one month. At 5 months there was an increase in bone formation and appearance of marrow with its accompanying marrow elements. There did not seem to be any evidence of major particle resorption, but there was evidence of osteoclastic activity. There was no evidence of acute or chronic inflammation. The pores in the particles permitted the early ingrowth of fibrous tissue and bone. In our experiment we also found that trabecular grew into the space between granules of calcium phosphate and direct contact with crystal granules.

Calcium phosphate is a kind of hard resorption material and separated granules. Calcium sulfate is the best binder for calcium phosphate. Once a composite of calcium sulfate and calcium phosphate is grafted into animals, calcium sulfate will be absorbed rapidly. This resorbed materials will supply the matrix of new bone formation and make a porous effect which will allow the new bone growing into space of granules of calcium phosphate and remodeling process to take place with gradual physiological timing [10,18-19]. On the other hand, calcium sulfate will promote the osteogenesis once it comes in contact with periosteum or bone. Although calcium phosphate is unable to promote osteogenesis, it is osteoconductive [20]. Our conclusions are that calcium sulfate will be absorbed rapidly and replaced by fatty tissue in bone marrow. Therefore it is not recommended as bone defect filler alone. A composite of calcium sulfate and calcium phosphate is considered as a good choice of bone defect filler.

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骨組織對硫酸鈣加磷酸鈣之吸收性和骨再生性比較分析研究

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摘　要

骨科手術中經常因骨折癒合不良、骨瘤、嚴重外傷或骨髓炎而需施行骨移植術，但臨床上往往難以取得足夠之海綿骨來配合手術，或因感染不適宜立即接受海棉骨移植，因而引發研究人員設法尋求替代物來協助醫師完成手術。這篇就是要以硫酸鈣及硫酸鈣和磷酸鈣之混合物植入大白兔脛骨骺內，觀察其吸收、骨化及骨組織之反應，做爲將來進人體實驗之基礎。我們將 6 隻紐西蘭大白兔分成三組，每組兩隻。分別於左右兩側脛骨近端內側海綿骨處植入硫酸鈣及硫酸鈣和磷酸鈣之混合物所製成的圓柱體，並分別飼養 6 週、12 週及 24 週後犧牲兔隻，取出標本在顯微鏡下觀察。實驗結果發現硫酸鈣對骨組織並沒有明顯的炎性反應，其一旦接觸骨膜或骨內膜等含有原生骨細胞時，則有明顯刺激骨增生作用，而骨髓內之硫酸鈣，因吸收過快，最終被結締組織或脂肪所取代，因此硫酸鈣並不適合單獨作爲骨移植替代物。磷酸鈣雖不具有骨增生作用，但有骨傳導支持作用，也不會引起明顯的炎性反應，因此和硫酸鈣混合後，利用硫酸鈣快速被吸收當作製造骨基質原料及產生空洞效果的特性，有利於新骨長入，所以這兩種材料結合後，彼此不同之特性相輔相成，因此硫酸鈣和磷酸鈣和混合物不失爲一理想的骨移植替代物。

關鍵詞：硫酸鈣、磷酸鈣、骨移植

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