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# Evaluation and Comparisons of Biodegradable Substances as Osteogenic Agents

A comparison and evaluation of biodegradable acid copolymers and ceramic both separately and chemically combined was done to determine osteogenic potential in rat tibias. All materials proved to be effective osteogenic agents and were tissue tolerant with a paucity of inflammatory effects. The ceramic - copolymer combine failed to provide additive advantages as had been hoped.
EVALUATION AND COMPARISONS OF BIODEGRADABLE SUBSTANCES AS OSTEOCGENIC AGENTS

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The replacement of bone segments of the jaws lost through trauma or disease poses a difficult problem in effective physiological resolution. Autogenous bone grafts provide the ideal solution, but the procurement of tissue often presents a considerable problem.

Polylactic acid (PLA) and polyglycolic acid (PGA) have been found to be nontoxic and non-tissue reactive substances which degrade slowly when implanted in the soft or osseous tissues of laboratory animals. These materials have versatility in that they can be cast into sheets, spun into fibers, or moulded into different shapes. The biologically degraded acids are entirely metabolized, primarily through the \( \text{CO}_2 \) in the respiration, without any vital organ accumulation.\(^1\) Studies performed at the United States Army Institute of Dental Research have shown that PLA and/or PGA can be effective in soft and hard tissue approximation and fixation. These biodegradable copolymers have been used in the repair of experimental fractures of the orbital floor\(^2\) and as intraosseous appliances in the treatment of mandibular fractures in dogs.\(^3\) The material has also been used in strand form as suture material for approximating soft tissues in the rat.\(^4\)

The role of ceramics in bone replacement has been well documented.\(^5\) Several types of degradable and non-degradable ceramic materials have demonstrated excellent tissue compatibility and have shown promise as a substitute for bone. The biodegradable ceramics such as tricalcium phosphate apparently undergo progressive phagocytosis by mesenchymal cells and are replaced by calcified bone tissue.\(^5\) The bone is formed directly on the latticework surface of the ceramic where it undergoes normal ossification.

Periodontal defects have been eliminated with tricalcium phosphate chips,\(^8\) and bone spaces filled with the substance were subsequently replaced by viable
It would appear from these earlier studies that both the acid copolymers and biodegradable ceramic are usable as tissue implants and bony replacements. The copolymers have been used in a supportive capacity on the basis of their strength and ease of manipulation. The degradation process however, is peripheral in nature with the core area resisting change until exposed directly after the more superficial material is biologically degraded and replaced. Conversely, it appears that the biodegradable ceramic, especially in powder form, degrades within the total volume at approximately the same rate allowing a relatively uniform osteogenesis throughout.

No attempt to directly compare these substances in an animal model has been done that we are aware of, nor has an attempt been made to biochemically combine PLA/PGA with tricalcium phosphate to determine compatibility and feasibility for usage. This study was designed to determine the comparative effectiveness of PLA/PGA and tricalcium phosphate in bone regeneration both singly and when combined.

Material and Methods

Forty-eight C.R. Nelson white male rats weighing approximately 400-425 grams each were utilized in this study. The animals were divided into four groups of twelve each and treated as follows:

Group 1: The animals were anesthetized with .02 cc sodium pentobarbital, both rear limbs shaved and the anteromedial surfaces of both tibias were exposed by dissection. An opening was made through the cortical bone into, but not through, the marrow space with a dental no. 8 round bur which created a defect of approx 1.5 cu. mm. Into this hole was placed an amount of a 50-50 mixture of PLA and PGA in solid spheroidal form. The overlying skin was returned to place and sutured at its original site. After recovery from the anesthesia the animals were returned to their cages, fed and watered ad libitium and four were sacrificed.
at 14, 28 and 42 days.

Group 2: The twelve animals in group 2 were treated in the same manner as those in group 1 except that tricalcium phosphate $\text{CA}_3 \left(\text{PO}_4\right)_2$ in finely ground powder form (<0.125 mm.) was deposited in the defects.

Group 3: The twelve animals in group 3 were also treated like group 1 except that a 50-50 mixture of $\text{CA}_3 \left(\text{PO}_4\right)_2$ and PLA/PGA was used. The ceramic powder was finely ground and dispersed in a 50-50 solvent mixture of hexa-flouroisopropynol and benzene to form a colloidal suspension with the copolymer. This was dropped in $N_2$ and freeze-dried to form solid spheroids which were deposited in the defects.

Group 4: Twelve rats were used as control animals. These were treated in the same manner as those in group 1 except that no implant was inserted into the defects.

Results

2 weeks: At 14 days bone formation was seen at all peripheries excepting the cortical plate in group 1 (Fig. 1). The central implant area presented isolated foci of fibroblastic proliferation but was primarily acellular with a peculiar biphasic homogenous appearance. Few inflammatory cells were noted. The group 2 specimens also had peripheral bone formation but the central area was totally filled with fibroblastic and osteoblastic proliferation in a uniform, orderly fashion reminiscent or lace of filligree. Inflammation was again conspicuously absent. It appeared that particles of implant material comprised the substance of central acellular areas (Fig. 2). Group 3 specimens exhibited peripheral ossification and a central area similar to group 1 with perhaps more numerous foci of fibroblastic and osteoblastic proliferation. The control group was well advanced in healing with osteogenesis projecting from the peripheries centrally although the cortical plate was not yet totally formed.

4 weeks: At 28 days group 1 specimens had additional bone formation in
peripheral areas with less evidence of implant material. Group 2 specimens had well-defined bone formation throughout the defect with small ovoid areas of implant remaining. The fine network of bone trabeculae was remarkable with bone formation occurring in accordance with the positioning of the implant material (Fig. 3). Inflammation was almost totally absent. Group 3 animals showed progressive healing and bone deposition from the peripheries to the center where homogenous implant was still present with cellular foci of osteoblastic and fibroblastic cells (Fig. 4). Controls were almost totally healed and marrow spaces had re-established themselves. The cortical bone was quite well moulded and only slightly irregular (Fig. 5).

6 weeks: At 42 days group 1 specimens displayed an almost total paucity of implant material although mature bone as such wasn't present in all central areas (Fig. 6). Cortical bone was well formed in most cases and throughout there was little evidence of inflammation or foreign body reaction. Marrow had not replaced bone and fibroblastic tissue in the central wound mass. Group 2 specimens were totally healed and marrow replacement was seen in isolated areas although the bone trabeculae were finer and more numerous than normal with less interbone space present for marrow replacement (Fig. 7). Group 3 specimens had good peripheral healing and cortical replacement but central areas still displayed implant material. Interestingly, several of these specimens had a supra-cortical hyperostosis of normal appearing bone which had assumed a conical shape. This was not seen in other experimental specimens (Fig. 8). The controls were well-healed, the cortex contoured, and hemopoetic marrow present.

Discussion

Early reports\textsuperscript{5-10} showed that tricalcium phosphate ceramics when inserted into bone were well tolerated and induced little inflammatory response. Other studies\textsuperscript{1-4} indicated good tissue tolerance of the copolymers such as PLA or PGA when used as mechanical support or for sutures, but the material resorbed for the most part from the periphery with tissue replacement on a "creeping" basis.
The ceramic, on the other hand, had a formative action whereby the particle surface served as a matrix on which osteogenesis could occur. It was felt that combining these compounds chemically such that the tricalcium particles were dispersed in the copolymer might allow a more uniform osteogenic pattern. The results were disappointing in that little cellular activity occurred within the mass and bone formation occurred peripherally not in much variance from the copolymers alone.

The compounds tested were uniform in their tissue compatibility as measured on the basis of inflammation and foreign body responses. It appears that the biological usefulness of these compounds rests with their individual properties. The repair of cranio-facial trauma or tumor surgery in an area in which these dual properties may well be utilized serves as a basis for further work ongoing at this institute at the present time.

Summary

An attempt was made to compare tissue responses between copolymers and ceramics in bone formation and to determine if the unique properties of each substance could be utilized if the compounds were chemically combined. The combination specimens behaved very little differently from the PLA/PGA specimens showing gradual healing from the peripheries progressing centrally. The tricalcium phosphate alone served as a format for osteogenesis with healing occurring simultaneously throughout the defect. All experimental materials were extremely tissue tolerant with very little inflammation or foreign body reaction occurring. The unique biological properties of PLA/PGA and tricalcium phosphate can best be utilized individually or simultaneously as separate units not biochemically combined.

Conclusion

This study reaffirms the remarkable biological compatibility of both biodegradable copolymers and ceramics but rules out the possibility of advantages when the compounds are chemically combined into a single substance in the proportions utilized in this experiment.
In conducting research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council.
BIBLIOGRAPHY

Illustrations

Fig. 1 - 50 Per cent polylactic acid and 50 Per cent polyglycolic acid at 14 days. (Magnification X33.) Implant (I) with peripheral bone proliferation and central acellular area.

Fig. 2 - Tricalcium phosphate at 14 days. (Magnification X400.) Central implant area with foci of ceramic (C) surrounded by fibroblastic and osteoblastic proliferation.

Fig. 3 - Tricalcium phosphate at 28 days. (Magnification X250.) Central implant area with osseous framework and remaining ceramic (C) foci.

Fig. 4 - Combination 50-50 PLA/PGA and Tricalcium phosphate at 28 days. (Magnification X100.) Implant (I) with peripheral and interweaving fibroblastic and osteoblastic (Arrows) activity.

Fig. 5 - Control at 28 days. (Magnification X40.) Operative area with incomplete cortical moulding and central marrow (M) replacement.

Fig. 6 - 50 Per cent polylactic acid and 50 Per cent polyglycolic acid at 42 days. (Magnification X100.) Implant area with mature bone, osteod (O), and remaining implant (I) material.

Fig. 7 - Tricalcium phosphate at 42 days. (Magnification X33.) Implant area with essentially total bone (B) formation and selective marrow (M) replacement.

Fig. 8 - Combination 50-50 PLA/PGA and Tricalcium phosphate at 42 days. (Magnification X33.) Cortical healing with supracortical hyperostosis (H) overlying central area in which biodegradable implant (I) material remains.