Load-bearing behavior of a simulated craniofacial structure fabricated from a hydroxyapatite cement and bioresorbable fiber-mesh

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Calcium phosphate cements (CPC) have proven successful in the repair of small, non-stress bearing skeletal defects. These cements do not have sufficient tensile strength or fracture toughness to allow their use in stress-bearing applications. It was hypothesized that a bioresorbable fiber mesh would improve the load-bearing behavior of shell structures fabricated of CPC. This study used a biaxial flexure fixture to compare the work-to-fracture values of discs made of: (1) CPC; (2) CPC reinforced with a bioresorbable two-dimensionally oriented poly(glactin) fiber-mesh; and (3) poly(methyl methacrylate) (PMMA) that were immersed in a serum-like solution for 0–28 days. CPC-mesh and PMMA discs were indistinguishable at 0, 1 and 7 days, based on work-to-fracture data. CPC and CPC-mesh discs were indistinguishable at day 28, because of fiber hydrolysis. The knitted fiber-mesh was effective in improving load-bearing behavior of a calcium phosphate cement for potential structural repair of bone defects.

1. Introduction

Cranial defects can result from craniocerebral trauma, neoplastic or inflammatory destruction, surgical removal, and congenital bone deformities [1]. Many materials have been employed to repair cranial defects, including autologous bone, hydroxyapatite and a variety of synthetic polymers. Despite their structural success most alloplastic materials remain as permanent foreign bodies [2].

Poly(methyl methacrylate) (PMMA) remains the most widely used synthetic material for cranial repair. Beneficial properties of PMMA have been reported to include low thermal and electrical conductivity, relatively high strength, radiolucency, ease of handling and inert biochemical properties [3]. Despite such advantages, PMMA implants can act as foreign bodies and become potential nidi of infection [4]. An inflammatory response, resulting in foreign body giant-cell formation and fibrous encapsulation of PMMA implants, has been consistently observed in animal studies of cranial defect repairs [5].

Calcium phosphate apatites have been identified as highly promising synthetic osteoconductive bone substitutes [6]. Calcium phosphate compounds are attractive because of their biocompatibility, chemical and physical resemblance to bone mineral [7] and the possibility of eventual replacement by bone.

Some calcium phosphates form hydroxyapatite crystals in a cementitious reaction not unlike the setting of gypsum products [8, 9]. One such cement, consisting of tetracalcium phosphate $(Ca_4(PO_4)_2O)$ and anhydrous dicalcium phosphate $(CaHPO_4)$ has been shown to form hydroxyapatite in an aqueous environment [9, 10]. The set calcium phosphate cement (CPC) consists of hydroxyapatite crystallites $(Ca_5(PO_4)_3OH)$ approximately 30 to 60 nm in width and up to 1 μm long [10]. Costantino and Friedman noted that CPC, when mixed with water, forms a dense paste that can be sculpted during surgery and isothermally converts to a microporous hydroxyapatite within 15 min, under physiological conditions [6].

Because of its apatitic nature, CPC is highly compatible with hard and soft tissues and has been tested for the direct surgical correction of small non-stress-bearing maxillofacial bony defects [5, 6, 9]. One study using CPC to reconstruct parietal skull defects in cats demonstrated progressive but variable replacement of the cement by new bone and soft tissue without a

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change in the shape or volume of the hydroxyapatite cement-reconstructed areas [5]. The physical properties of CPC are not sufficient to allow its use in large defects or stress-bearing locations and monolithic CPC structures are not advocated for extensive cranial deficiencies or reconstruction of small thin bones (e.g. malar bones).

Cementitious materials are also amenable to indirect processes using common laboratory techniques, such as those used when fabricating large PMMA cranial implants on gypsum replicas of the patient's defect. As opposed to direct surgical placement, indirect fabrication allows optimum control over aesthetics and material quality while allowing considerable engineering latitude in developing novel CPC-based structures, e.g. with oriented fiber reinforcement. Fiber-toughened composite materials are well known in both engineering and biomedical usage. In cases where stresses are primarily oriented linearly or biaxially, oriented fibers can provide an enhancement of physical properties beyond that engendered by randomly directed fibers.

Because many maxillofacial structures are primarily thin shell structures subjected to relatively simple loading (e.g. malar, orbital and cranial bones), it is conceivable that even a single layer of two-dimensionally oriented fibers may provide a significant structural advantage. Poly(glactin) mesh, a copolymer of poly(glycolic) and poly(lactic) acids, has been shown to have many desirable characteristics as a dural grafting material, because it is: (1) easily handled, (2) relatively inexpensive, (3) bioresorbed over time, and (4) elicits both a minimal inflammatory response and minimal adhesion formation [2, 11]. Both a loosely knitted and tightly woven poly(glactin) fiber-mesh have shown potential as resorbable dural substitutes [2, 11]. Poly(glactin) produced the best results, compared to poly(glycolic acid), silk, and poly(ester) suture materials, for closure of the dura mater with respect to the smoothness of the subdural surface, the presence of adhesions between sutures and the brain surface, the degree of absorption of the material, and tissue reaction [12].

The purpose of the present study was to process and evaluate the fracture behavior of shell structures (discs) fabricated of (1) CPC, (2) CPC incorporating poly(glactin) fiber-mesh and (3) PMMA. It was hypothesized that the bioresorbable fiber mesh would improve the load-bearing ability of CPC discs tested in biaxial flexure. Biaxial flexure was chosen over uniaxial bend bar testing as better representing the loading expected clinically for edge-supported prostheses. Such fiber-reinforced CPC discs would be highly anisotropic and their failure would be expected to be complex, conditions for which no standard toughness tests exist and for which simple strength tests are inappropriate. Work-to-fracture in biaxial flexure was measured over a displacement of 2 mm and results compared among groups using ANOVA and a 95% multiple range test.

2. Materials and methods

Knit and woven sheets of resorbable poly(glactin) 910 fibers [poly(glycolic acid) and poly(lactic acid)] were supplied by the manufacturer (Vicryl 910®, Ethicon Inc., Somerville, NJ) (Figs 1 and 2). Poly(glactin) 910 is a random copolymer containing 90% glycolide and 10% lactide units having an average molecular weight of 50 000. Fibers are 17 μm in diameter with 2 deniers per filament. The CPC powder used (ADA Paffenbarger Research Center, NIST, Gaithersburg, MD) consisted of dicalcium phosphate (anhydrous) (mass fraction of 27.2%) having a mean particle size of 0.7–1.2 μm and tetracalcium phosphate (mass fraction of 72.8%) with a mean particle size of 13–18 μm. In preliminary work 10 specimens were fabricated (as described below) using the loosely knitted mesh and an additional 10 specimens were fabricated using the tightly woven mesh. For the powder size used, a water slurry paste of CPC would not adequately penetrate into the tightly woven mesh and only the knitted mesh was investigated further.

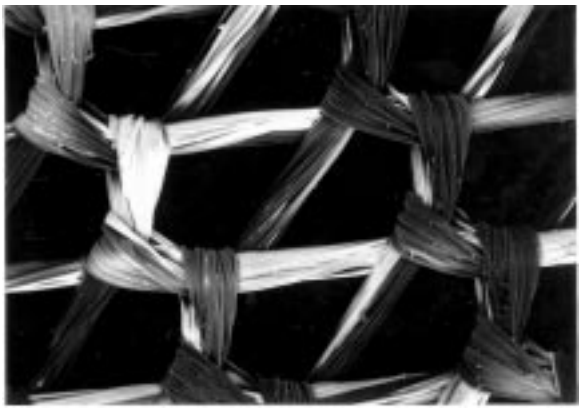

Figure 1 Photomicrograph of woven poly(glactin) mesh (scanning electron microscopy; SEM original magnification × 50).

Figure 2 Photomicrograph illustrates knitted poly(glactin) mesh organization (SEM original magnification × 50).

Disc-shaped 15 × 2 mm CPC-containing specimens were prepared by mixing CPC powder and water with a powder/liquid mass ratio of 4:1 and packing this paste into Teflon molds. Knitted poly(glactin)/CPC specimens were prepared by placing 15 mm diameter sections of the knitted mesh into molds (on the intended tensile surface) prior to filling the molds with the cement. Molds were slightly over-filled, excess cement was expressed beneath glass cover plates held by ''c''-clamps, and molds were stored at 37 °C and 100% humidity. Specimens were removed from the molds after 24 h and stored under ambient conditions.

TABLE I Test group designations

Material groups	Code
CPC, day 0	CPC-0
CPC, day 1	CPC-1
CPC, day 7	CPC-7
CPC, day 28	CPC-28
CPC-mesh, day 0	CPC-m-0
CPC-mesh, day 1	CPC-m-1
CPC-mesh, day 7	CPC-m-7
CPC-mesh, day 28	CPC-m-28
PMMA, day 0	PMMA-0
PMMA, day 28	PMMA-28

PMMA specimens, 15 × 2 mm, were made by mixing clear, heat-processed, acrylic resin polymer and methyl methacrylate monomer (Robert B. Scott Ocularists of Florida, Inc., Tampa, FL) in a powder/liquid ratio of 3 : 1 by volume and packing the resulting dough into the Teflon molds. Molds were slightly over-filled, excess PMMA was expressed beneath glass cover plates held by ''c'' clamps. Polymerization was achieved by placing the prepared molds in a container of cold water and bringing the water temperature to 100 °C for 20 min. Specimens were removed from the molds following polymerization and stored under ambient conditions.

Specimens were arbitrarily assigned to 10 experimental groups based upon the material and storage condition combinations to be evaluated. At least 10 specimens were prepared for each of the groups listed in Table I.

An aqueous electrolyte solution was formulated having a serum-equivalent saturation ratio with respect to hydroxyapatite (saturation ratio = 9.39) and buffered to pH 7.25 with HEPES (*N*-[2-hydroxyethyl]piperazine-*N*′-[2-ethanesulphonic acid]) (Sigma Chemical Co., St. Louis, MO). The composition of this artificial serum solution is given in Table II. Such a serum-equivalent solution, unlike simple saline, provided for the possibility of additional apatite formation during the storage period while avoiding the possibility of apatite dissolution. CPC specimens were arbitrarily assigned to groups for testing following immersion in the serum solution at 37 °C for 0, 1, 7 or 28 days and PMMA discs for 0 or 28 days. At least nine specimens were used for each selected storage interval.

Testing was performed in biaxial flexure using a ring-on-ring fixture (Fig. 3) in a universal testing machine at a crosshead speed of 0.5 mm min^{-1} (United Calibration Corporation, Huntington Beach, CA). Within the context of this study, work-to-fracture was defined (and

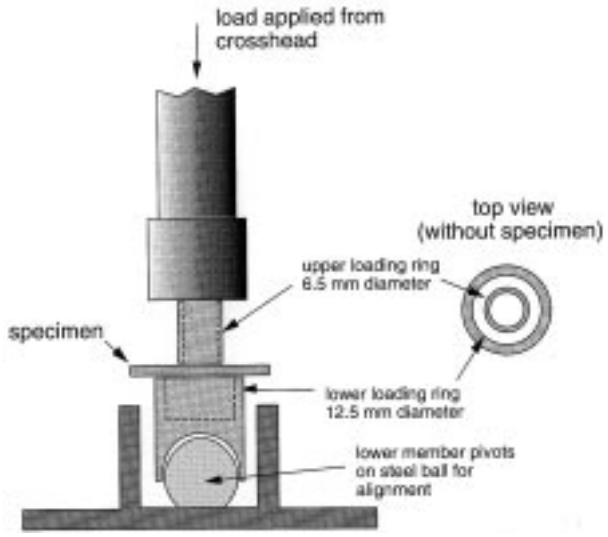

Figure 3 Schematic of ''ring-on-ring'' biaxial flexure test fixture.

measured) as the area under the load–displacement curves, up to a total crosshead displacement of 2 mm. An end-point crosshead displacement of 2 mm for the CPC-mesh group was not chosen arbitrarily. First, beyond 2.5 to 3.0 mm loads began to increase due to artificial mechanisms including wedging of portions of broken specimens within the apparatus. Thus an equivalent end-point, zero load held, could not be reached. Second, it was also considered that displacement beyond 2.0 mm had little clinical significance. Third, displacements from (approximately) 0.5 mm up to 2 mm were considered important, because the CPC-mesh specimens were still supporting significant loads, unlike the PMMA or CPC specimens, and this performance should not be ignored. Fourth, since the displacement for complete failure would have been well beyond 2 mm, the CPC-mesh numbers are actually quite conservative. It should also be considered that no standard criteria exist for the clinical performance of cranial implants.

Areas were measured using a digitizing pad and dedicated software (Bioquat System IV, R & M Biometrics, Inc., Nashville, TN). Three area measurements were made and averaged for each load-displacement curve. Work-to-fracture values were evaluated among groups using a Kruskal–Wallis analysis and Tukey's Studentized range test. Specimen thickness (t) was measured using a digital micrometer (Digimatic, Mitutoyo Corp., Japan). Values of t and t^2 were analyzed using ANOVA to assure that no significant differences existed among groups found to differ in work-to-fracture.

TABLE II Serum equivalent solution (mmol l^{-1} in deionized water)

Ionic species	Concentration	Ionic species	Concentration
Cl	102.94	K	4.94
KCl	5.93×10^{-2}	KOH	2.14×10^{-7}
H_2CO_3	2.35	HCO_3	24.30
CO_3	0.05	Ca	2.19
$CaHCO_3$	0.18	$CaCO_3$	1.64×10^{-2}
CaOH	3.5×10^{-6}	$Ca(OH)_2$	1.20×10^{-10}
Mg	1.31	MgCl	4.60×10^{-3}

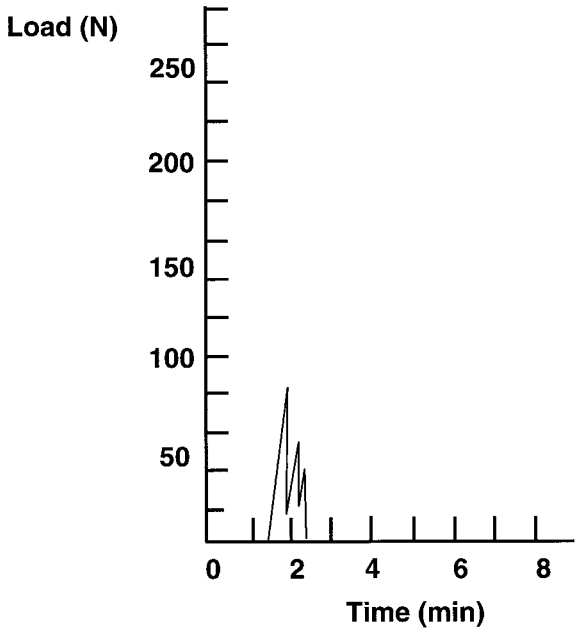

Figure 4 Representative load-time behavior for CPC discs. Peaks represent individual fracture events. Total area under load–displacement curves was used to calculate work-to-fracture. Loading was halted upon complete failure of CPC discs.

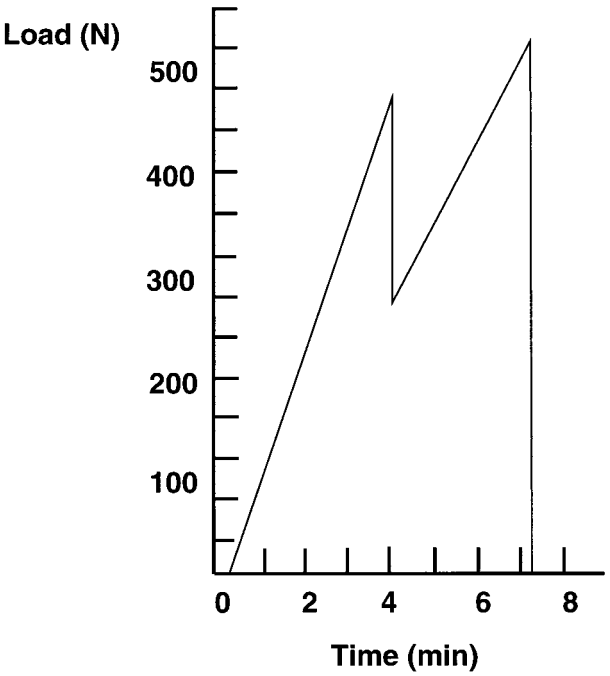

Figure 5 Load–displacement behavior of a representative PMMA disc (note that the scale differs from Figs 4 and 6).

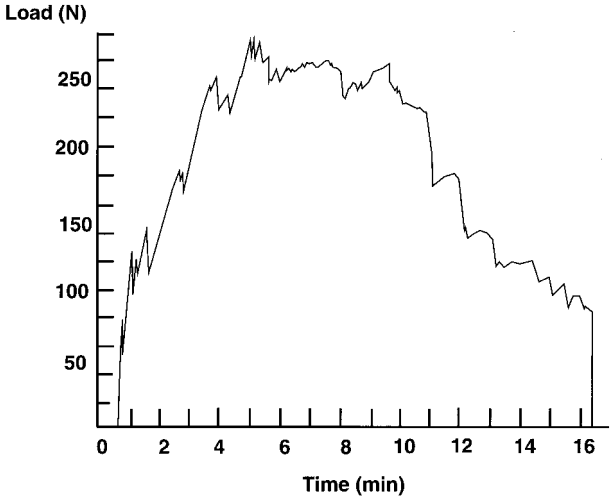

Figure 6 Load–displacement response of a characteristic CPC-mesh specimen demonstrating the toughening effect of fiber networks. Note that much higher loads were achieved compared to Fig. 4, and that high loads were maintained even though numerous fracture events occurred. Loading was halted after 2 mm of crosshead displacement in the CPC-mesh disc.

TABLE III Work-to-fracture means (in Ncm) and standard deviations

Group	*N*	Mean	SD	Homogeneous groups*
CPC-m-28	11	0.28	0.12	}
CPC-0	9	0.31	0.09	
CPC-1	10	0.31	0.39	
CPC-28	10	0.35	0.25	
CPC-7	10	0.36	0.34	
PMMA-28	10	21.45	7.46	}
CPC-m-1	10	22.65	2.98	
CPC-m-7	11	23.21	3.07	
PMMA-0	10	28.61	13.60	
CPC-m-0	10	29.10	3.83	

*Brackets group means that do not differ (Tukey's Studentized range test, $P = 0.05$).

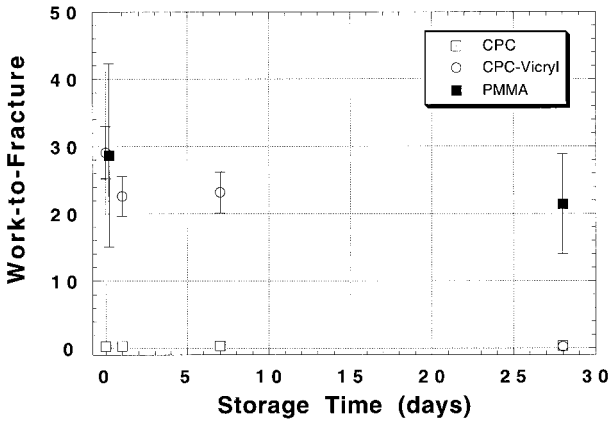

Figure 7 Work-to-fracture means and standard deviations plotted as a function of storage time (standard deviations for CPC means are not visible, being smaller than plotted symbols).

3. Results

Characteristically different load–time responses were found for each material (CPC, PMMA, and CPC-mesh), as illustrated in Figs 4, 5 and 6, respectively. CPC (Fig. 4) behaved as a simple brittle material having a comparatively low apparent fracture toughness (related to the area beneath the load-displacement curve). The PMMA discs (Fig. 5) demonstrated higher apparent toughness and held higher loads than CPC discs before failure. CPC-mesh specimens (Fig. 6) progressed to failure in a manner consistent with the inelastic behavior of oriented fiber composites, holding relatively high loads even as innumerable fracture events occurred [13].

Means, standard deviations (SDs) and statistical groupings appear in Table III. Mean work to fracture values are plotted in Fig. 7 as a function of storage time. Two groups emerged as being statistically distinct ($P < 0.0001$, Kruskal–Wallis; 95% Tukey's performed

on transformed data, N $m^{0.2}$, due to the highly unequal variances). All of the CPC specimens without fiber reinforcement, plus the 28 day CPC-mesh, belong to the lowest work-to-fracture group. Significantly higher work-to-fracture was recorded for the remaining CPC specimens with mesh and the PMMA discs. CPC-m-0 and CPC-m-1 groups were found to differ when compared pairwise (Student's t-test, $P < 0.0004$). There were no differences in either t or t^2 among groups to account for work-to-fracture measurement distinctions ($P > 0.05$, ANOVA, Tukey's).

4. Discussion

Ring-on-ring biaxial flexure testing, well described for obtaining tensile strength data [14], was used in this study for a number of reasons. This loading arrangement minimized contact stresses, allowing the tougher specimens to continue carrying loads without having the fixture ''punch through'' the disc. Such ''punch through'' was encountered in pilot work using a piston-on-ball fixture. Standardized toughness tests [15] were not considered appropriate since a highly heterogeneous ''structure'' was being tested as opposed to a homogeneous material. The structure being tested had inherent anisotropies derived from both its design and the fiber-mesh component. The toughening fiber-mesh was incorporated into only one surface, since it was assumed that clinical loading of implants would occur in such a manner as to create the highest tensile stresses on the internal surface of ''shell like'' structures. Equally important, discs could be fabricated for testing in a similar fashion to the structure being modeled (e.g. a cranial plate), which helps to assure some comparability with respect to processing-related structural defects [16].

For up to seven days in the serum electrolyte solution at pH 7.25, the CPC-mesh discs performed as well as acrylic resin (stored for either 0 or 28 days) as judged by the work-to-fracture test used. Obviously, the choice of a 2 mm displacement end-point influences any comparison with acrylic. Acrylic specimens held higher loads before failure, but did not continue to sustain load-bearing ability following fracture. Although the loads for initial crack development in all CPC specimens appear to be similar (first load drop in Figs 4 and 6), the bidirectionally orientated poly(glactin) fibers resisted the biaxial tensile stresses and very good adhesion was exhibited between the cement and fibers, improving the mechanical properties of the CPC-matrix structure. By 28 days, the poly(glactin) mesh was no longer capable of providing increased toughness. In addition, the degradation of fibers left 75–180 μm defects in the tensile surface of the CPC disc which could certainly be expected to decrease the load required for catastrophic crack initiation.

Tensile strengths of Vicryl suture material have been measured as a function of aqueous storage times at various levels of pH [17]. Vicryl best retained tensile properties at pH 7.44, with 95% of its base strength retained at 7 days but dropped to 10% of base strength by 28 days [17]. These findings closely parallel those of the present study, indicating that decreases in mesh tensile strength changes due to aqueous storage were very likely responsible for the disc work-to-fracture degradation over very similar times. The CPC did not appear to either retard or accelerate the hydrolytic degradation of poly(glactin) fibers. Although physiological conditions are undoubtedly more complex than those recreated in laboratory studies, the *in vivo* degradation of poly(-glactin) suture material may be strongly dependent only on the activity of water (at an appropriate pH). For example, in one *in vivo* study in which sutures were inserted into rat scapular and sacral subcutis sites, Craig *et al.* report very similar percentages in breaking strengths for retrieved Vicryl sutures that had been implanted for 7 and 28 days [18].

This study demonstrated that bioresorbable fiber networks, based upon poly(glactin), are clearly compatible as a potential reinforcement phase in calcium phosphate cements. Fiber-reinforced CPC structures warrant closer inspection as stress-bearing craniofacial implants, using fibers chemically and structurally tailored to provide more appropriate degradation times. Technology is also becoming available for the incorporation of specific cytokine growth factors within fiber networks, which could provide bone replacement materials that guide the development of normal tissue architecture while maintaining structural capability.

5. Conclusions

The following conclusions were drawn within the limits of this study.

1. As hypothesized, the bioresorbable poly(glactin) fiber-mesh influenced the load-bearing behavior of shell structures fabricated of CPC.
2. All of the CPC specimens without fiber reinforcement along with the CPC-mesh specimens stored for 28 days belonged to the lowest work-to-fracture group. Significantly higher work-to-fracture was recorded for the remaining CPC-mesh specimens and the PMMA discs.
3. For up to 7 days, the CPC-mesh group performed as well as the control PMMA group as judged by the conditions and test used.
4. By 28 days the poly(glactin) mesh was no longer capable of providing increased toughness.

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Certain commercial materials and equipment are identified in this article for adequate definition of the experimental procedure. In no instance does such identification imply recommendation or endorsement

by the National Institute of Standards and Technology or the Department of Defense, or that the material or equipment is necessarily the best available for the purpose.

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