Pulpotomy therapy in primary teeth: new modalities for old rationales

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Abstract

Pulpotomy therapy for the primary dentition has developed along three lines: devitalization, preservation, and regeneration. Devitalization, where the intent is to destroy vital tissue, is typified by formocresol and electrocautery. Preservation, the retention of maximum vital tissue with no induction of reparative dentin, is exemplified by glutaraldehyde and ferric sulfate treatment. Regeneration, the stimulation of a dentin bridge, has long been associated with calcium hydroxide. Of the three categories, regeneration is expected to develop the most rapidly in the coming years. Advances in the field of bone morphogenetic protein (BMP) have opened new vistas in pulp therapy. Human BMPs with dentinogenic properties are becoming available through recombinant technology. We are now entering an era of pulpotomy therapy with healing as the guiding principle. (Pediatr Dent 16:403–9, 1994)

Introduction

No area of treatment in pediatric dentistry has been more controversial than pulp therapy. In particular, the vital pulpotomy procedure has been a topic of debate for decades. While pulpotomy therapy evolved slowly over the first 40 years, the pace of change since the 1960s has continued to accelerate. This article is a review and prospectus of this field, presented in the context of the rationales that have guided development of new and very divergent treatment modalities. While there have been many excellent reviews of pulp therapy in recent years,[1–4] none has presented a framework for the systematic analysis of past developments or future trends. A simple chronological detailing of the advances in pulpotomy therapy without an attempt to categorize the underlying mechanism of action, does not permit the clinician to adequately weigh the pros and cons of current and future treatment options.

Pulpotomy therapy can be classified according to the following treatment objectives: devitalization (mummification, cauterization), preservation (minimal devitalization, noninductive), or regeneration (inductive, reparative). Based on this premise, a chronological and classified list of significant studies is presented in Table 1. This format categorizes research related by treatment objectives; it unfolds continuums of effort that show where the future lies. Not all the studies listed in Table 1 are directly related to new or modified modalities; some are included because they awakened the profession to the possible toxicity of certain pulpotomy agents, thereby altering the status quo.

Devitalization

The first approach to pulpotomy treatment of primary teeth was devitalization. The multiple-visit formocresol technique, as introduced by Sweet,[5] was designed to mummify the tissue completely. When completely fixed, the radicular pulp was theoretically sterilized and devitalized, thereby obviating infection and internal resorption. Apparently this protocol was highly successful.[6] However, Sweet reduced the number of visits over the years, presumably because of economic and behavior management considerations, and in 1962, in affirmation of a common practice, Doyle et al.[7] used a two-visit procedure in their comparison study of formocresol and calcium hydroxide. Within a few years, Spedding et al.[8] and Redig[9] reported the results of a 5-min formocresol protocol, and since that time, complete mummification has been abandoned by the profession.

Following the initial clinical trial by Redig,[9] the 5-min treatment with formocresol became, and has remained, the standard against which all new modalities are compared. However, the original advantage of complete mummification — sterilization and metabolic suppression — was lost. Instead, the short treatment leaves the pulp only partially devitalized. Commonly, the pulp remains half dead, half vital, and chronically inflamed.[10] In this state, the pulp is susceptible to abscess formation, and the root to internal resorption. As such, the only rationale for using formocresol is empirical — it succeeds more often that it fails. Reducing the concentration of formocresol used in pulpotomies, spurred by a series of toxicity[11–13] and systemic distribution studies,[14, 15] has served only to move us further from the original objectives. While reducing formocresol is laudable,[16] using a diluted form merely extends the empiricism. Despite half a century of research, we are still unable to explain why two toxic agents such as formaldehyde and cresol can be used beneficially.

In an attempt to avoid chemicals altogether, Judd and Kenny[17] have suggested pulpectomies as standard care for all pulpally involved carious teeth. This mo-

Table 1. Evolution of the pulpotomy procedure in primary teeth

	Devitalization	*Preservation*	*Regeneration*
1930	*Multiple Visit FC Pulpotomy* Human (Sweet, 1930)		
1938			*CaOH Pulpotomy for Primary Teeth* Human (Teuscher & Zander, 1938)
1960			
1961			
1962	*2 Visit FC Pulpotomy* Human (Doyle et al., 1962)		
1963			
1964			
1965	*5-min FC Pulpotomy* Animal (Spedding et al., 1965)		
1966	Human (Redig, 1966)		
1967			
1968			
1969			
1970	*Dilution of FC* Animal (Straffon & Han, 1970)		*CaOH Evaluated* Human (Magnusson, 1970)
1971	(Loos & Han, 1971)	*ZOE Evaluated* Human (Magnusson, 1971) *Ledermix Introduced* Human (Hansen et al., 1971)	
1972			
1973			
1974			
1975	*Dilution of FC* Human (Morawa et al., 1975)	*Glutaraldehyde Proposed* Root Canals (S'Gravenmade, 1975)	
1976			
1977			
1978	*Systemic Distribution of FC* Animal (Myers et al., 1978)	*Gultaradehyde Proposed* Pulpotomy (Ranly & Lazzari, 1978)	
1979			
1980		*GA Pulpotomy* Human (Kopel, 1980)	
1981	*Dilution of FC* (Omission from ZOE) Animal (Godoy, 1981)		
1982			
1983	*Systemic Effects of FC* Animal (Myers et al., 1983) *Electrosurgical Pulpotomy* Animal (Ruemping et al., 1983)		
1984			*Enriched Collagen* Animal (Fuks et al., 1984) *Hard Setting CaOH* Human (Heilig et al., 1984)
1988			*Freeze Dried Bone* Animal (Fadavi et al., 1988)
1989			*Demineralized Dentin* Animal (Nakashima, 1989)
1990			
1991	*ZOE Pulpectomy* Human (Judd & Kenny, 1991)	*Ferric Sulfate* Human (Fei et al., 1991)	*Bone Morphogentic Protein* Animal (Nakashima, 1991)
1992			
1993	*Electrosurgical Pulpotomy* Human (Mack, 1993)		*Osteogenic Protein (OP-1)* Animal (Rutherford et al., 1993)
Future	Laser Therapy?	?	OP1 and/or other factors

dality eradicates all radicular tissue, and, in a sense, returns to the original Sweet philosophy of absolutism. The success rate of pulpectomies in posterior teeth was reported to range from 67 to 91%, depending upon the stringency of the evaluation.[18] Although the authors concluded that ZOE pulpectomies are at least as effective as formocresol pulpotomies, the demanding nature of the procedures might dissuade the profession from adopting their philosophy of pulp care.

Another form of nonchemical devitalization emerged during the last decade: electrosurgical pulpotomy.[19-23] Whereas mummification eliminates pulp infection and vitality with chemical crosslinking and denaturation, electrocautery carbonizes and heat denatures pulp and bacterial contamination. Electrosurgery does little to improve on the formocresol pulpotomy save avoiding chemicals. Experimentally, electrosurgery has been shown to incite pathologic root resorption and periapical/furcal pathology[21] and a spectrum of pulpal effects including acute and chronic inflammation, edema, fibrosis, and diffuse necrosis.[22] It may prove to be more diagnosis and technique sensitive, and it may not be suitable if apical root resorption has occurred.[20] Remarkably, Mack and Dean[23] reported a very high success rate with the technique. It is difficult to explain why burned tissue is tolerated by the residual vital pulp. Nonetheless, despite the bleak histologic picture and perpetuated empiricism, electrosurgery will undoubtedly gain in popularity.

In the future, laser energy might be able to overcome the histologic deficits of electrosurgery. Ideally, laser irradiation would create a superficial zone of coagulation necrosis that remained compatible with the underlying tissue and that isolated the pulp from the vagaries of the subbase. Thus far, only exploratory research has been done with lasers in pulp therapy.[24, 25]

Preservation

Included in this category is a potpourri of modalities intended to only minimally insult the tissue. While not capable of initiating an inductive process, each was proposed as a way to conserve virtually all of the radicular pulp. One might contest including in this category agents such as glutaraldehyde and ferric sulfate that obviously effect superficial tissue changes, but I argue that they differ from formocresol and electrosurgery by virtue of their properties, actions, and rationale for use.

Zinc oxide-eugenol (ZOE) was the first agent to be used for preservation. Because this cement was such a workhorse in early dentistry, it is little wonder that it was adapted to pulpotomies. But because it was so popular, we will probably never know who initiated the practice. While earlier studies revealed some negative aspects of ZOE pulpotomies, it was the comprehensive histologic analysis by Magnusson[26] that best demonstrated the resultant inflammation and internal resorption. We now know that eugenol possesses destructive properties,[27] and cannot be placed directly on pulp.[26] Although an obtundent, ZOE does not apparently suppress metabolism adequately or self-limit its irritative properties.

Table 2. Clinical studies with glutaraldehyde

Investigators	*Clinical Success Rate (%)*	*Radiographic Success Rate (%)*	*Duration (months)*
1. Garcia-Godoy	100	98	42
2. Alcam	96	92	12
3. Guiliana	96	96	12
4. Prakash et al.	100	100	6
5. Fuks et al.	96	82	25
6. Tsai et al.	98	78.7	36

In an effort to overcome the internal resorption seen in ZOE and calcium hydroxide pulpotomies, a dressing containing a corticosteriod was evaluated clinically.[28] While the steroid reduced the inflammation and internal resorption when compared with ZOE, the degree of improvement and the success rate (79%) were not remarkable.

In recent years, glutaraldehyde has been proposed as an alternative to formocresol based on: its superior fixative properties,[29] self-limiting penetration,[30] low antigenticity,[31] low toxicity,[32] and the elimination of cresol.[33] The histologic picture of a glutaraldehyde-treated pulp shows a zone of superficial fixation with very little underlying inflammation.[34-36] The clinical success rates with glutaraldehyde have ranged widely[37-42] (Table 2). The variability is perhaps a reflection of the wetness of the pellet applied to the radicular tissue. Studies in which it is known that glutaraldehyde was not overzealously blotted from the pellets before use have shown high success rates.[37,40] It has been observed that inadequate fixation leaves a deficient barrier to subbase irritation, resulting in internal resorption.[43,44]

A nonaldehyde chemical, ferric sulfate, has received some attention recently as a pulpotomy agent.[45,46] This hemostatic compound was proposed on the theory that it might prevent problems encountered with clot formation and thereby minimize the chances for inflammation and internal resorption. It has not been explained how clotting itself could curtail these activities. Possibly the metal-protein clot at the surface of the pulp stumps acts as a barrier to the irritative components of the subbase. If true, the ferric sulfate may function solely in a passive manner. An earlier 12-month clinical evaluation of ferric sulfate pulpotomies[46] showed an excellent success rate, but the results reported from a more recent study were considerably less favorable.[47] That heavy metal coagulation with ferric sulfate is somehow able to subdue the pulp when the high pH-coagulation of calcium hydroxide cannot, remains to be verified.

This category of pulp therapy is still in flux, although major changes in the future are not likely. We may seem to have temporarily exhausted our store of chemicals that can be applied to pulp tissue, but someone somewhere will go on looking for the perfect drug.

Regeneration

Surely we agree that the ideal pulpotomy treatment should leave the radicular pulp vital and healthy and completely enclosed within an odontoblast-lined dentin chamber. In this situation, the tissue would be isolated from noxious restorative materials in the chamber, thereby diminishing the chances of internal resorption. Additionally, the odontoclasts of an uninflamed pulp could enter into the exfoliative process at the appropriate time and sustain it in a physiologic manner. Implied in this scenario is the induction of reparative dentin formation by the pulpotomy agent. Unlike the other two categories for pulp treatment, the rationale for the developing field of regeneration is actually based on sound, biologic principles. In 1972, Boller[48] published an article in which he called his era of pulpotomy treatment the "Biological Era." In truth, we are only now entering it.

Calcium hydroxide was the first agent used in pulpotomies that demonstrated any capacity to induce regeneration of dentin.[49] Even from the first, however, it was observed that the procedure was not always successful. In retrospect, it was serendipitous that calcium hydroxide was effective at all. The rationale that prompted its use by Zander was fundamentally erroneous. He attributed the action of calcium hydroxide to a modification of the solubility product of Ca and PO^4 and a precipitation of salt into a organic matrix. Ignored was the origin of this matrix and how odontoblast processes became included in it. More likely than not, the high pH of calcium hydroxide wounds the pulp in a manner that permits the intrinsic reparative cascade to begin. Unfortunately, the stimulus evoked by this compound is delicately balanced between one of repair and one of resorption. The study by Magnusson[50] demonstrated how often the balance is tilted toward the destructive pathway.

The popularity of calcium hydroxide has ebbed and flowed. It is considered a safe drug relative to formocresol, but, other than that, there are no strong arguments for its use. A more recent study,[51] in which a hard-setting calcium hydroxide cement was used instead of the inorganic compound, showed a higher success rate. However, the pulpotomized teeth were followed for only 9 months. Whether calcium hydroxide in a cement vehicle can elicit more favorable responses remains to be determined.

Fortunately, the era of chemicals like calcium hydroxide may be coming to an end. Recent advances in the field of bone and dentin formation have opened exciting new vistas for pulp therapy, and we are fast approaching a rational period in the treatment of pulp tissue. We now have the prospect of being able to induce reparative dentin with recombinant dentinogenic proteins similar to the native proteins of the body.

This exciting new era is founded on two classic observations made many years ago. Huggins[52] noted that urinary tract epithelia implanted into the abdominal wall of dogs evoked bone formation. Some years later, Urist[53] observed that demineralized bone matrix stimulated new bone formation when implanted in ectopic sites such as muscle. Urist concluded that bone matrix contains a factor capable of autoinduction, and he named this factor bone morphogenetic protein (BMP). Since that time, countless labs have attempted to purify the factor, or factors, but because it exists in such minute quantities and has such a high affinity for the bone matrix, progress has been slow. Only very recently, with techniques of molecular biology, has significant progress been made. We now know that there is a family of proteins that has bone inductive properties, and BMP is a generic term for this family.[54]

The quest for BMP is not an esoteric exercise. The ramifications of a commercially available factor that can predictably induce bone for use in the fields of orthopedic, oral, and periodontal surgery are mind boggling. The implications for pulp therapy are also enormous. If BMP can induce dentin as well as bone, dentists might at last have a true biological pulp-capping and pulpotomy agent. Such a possibility was suggested by the observation that demineralized dentin also can induce bone when implanted in ectopic sites.[55] Recent experiments have, in fact, demonstrated that BMP from both bone and dentin will promote dentinogenesis.[56, 57]

BMPs are members of a highly conserved family of signaling molecules that have been used repeatedly during evolution to mediate tissue interactions during embryonic development.[58] Because they were discovered in phylogenetically lower organisms, a confusing multiplicity of names has arisen. In addition, the term

Table 3. The DVR family of TGF-ß-related proteins*

Mammalian	*Xenopus*	*Drosophila*
		DPP/DVR-15
	DVR-1/Vg1	
DVR-2/BMP-2/BMP-2a	DVR-2	
DVR-3/BMP-3/osteogenin	DVR-3	
DVR-4/BMP-4/BMP-2b	DVR-4	
DVR-5/BMP-5	DVR-5	
DVR-6/BMP-6/vgr-1	DVR-6	
DVR-7/BMP-7/OP-1	DVR-7	
	DVR-8-14	
OP-2		
VgR-2 plus three others		

* Modified from Lyons et al.[57]

Table 4. Bone morphogenetic proteins

	BMP-2	*BMP-3*	*BMP-4*	*BMP-5*	*BMP-6*	*BMP-7*	*OP-2*
Alternate names	*(BMP-2A)*	*(Osteogenin)*	*(BMP-2B)*		*(VgR-1)*	*(OP-1)*	
Ectopic implant	*Bone*	*Bone*	*Bone*	*Bone*		*Bone*	*Presumed*
Pulp dressing	*Osteo & Tubular Dentin*•	*Osteo-Tubular Dentin*				*(OP-1) Osteodentin (BMP-7) Osteo & Tubular Dentin*•	*?*
Source for experimentation†	*Bovine rH*	*Bovine rH*	*rH*	*rH*	*rH*	*Bovine rH*	*rH*

• Crude preps of bovine bone containing BMP-2, BMP-3, BMP-7 and possibly others.

† rH = Recombinant human.

BMP is misleading in that it implies a single gene product responsible for osteogenesis, when, instead, each probably accounts for multifunctional gene products expressed throughout embryonic development.

To bring some order to the chaos, this family of proteins has been renamed the DVR (decapentaplegic-Vg-related) family, based on the first two members to be identified—*Drosophila* decapentaplegic and *Xenopus Vg1*. Table 3 lists the family by DVR, BMP, and osteogenic protein (OP) names. The DVR family belongs to the much larger transforming growth factor ß (TGF-ß) superfamily that includes five TGF-ßs, activins, inhibins, and the Müllerian-inhibiting substance. These secreted proteins are characterized by a highly conserved carboxyterminal region rich in cysteine residues used for dimerization.

Table 4 lists the known BMPs and their actions when implanted into receptive tissue. Most of the proteins were evaluated for osteogenic potential in vivo following subcutaneous implants in rats. Pulp responses to various preparations were determined in dog and primate teeth. These activities suggest a role for these proteins in healing bone and pulp. However, as mentioned above, each probably has other functions during embryogenesis. For instance, BMP-4 recently has been shown to be associated with epithelial/mesenchymal interactions during early tooth development.[59] And OP-1 mRNA is expressed mainly in the kidneys and bladder,[60] which might explain why the urinary tract epithelia implanted into muscle by Huggins[52] evoked bone formation. While the developmental and postdevelopmental roles of these proteins have only begun to be explored, their ability to promote bone healing is being used to advantage.[61–63] Importantly for dentistry, these osteogenic proteins hold promise for pulp therapy.

Although tightly associated with collagen of matrix, the BMPs are classified as noncollagenous proteins. An attempt by Fuks et al. to use collagen alone as a dressing for pulpotomized teeth of primates was unsuccessful.[64] Because collagen is an integral constituent of dentin and bone matrix, the investigators reasoned that it could serve as a template to spur reparative dentinogenesis. But collagen devoid of BMP has no osteogenic potential and simply is resorbed. As a consequence of these studies, collagen has been used as a neutral carrier for the BMPs in assays, orthopedic surgery, and pulp experimentation, so it is not surprising that it failed to initiate dentinogenesis.

Capitalizing on the early knowledge that demineralized bone and dentin are inductive, Fadavi et al.[65] dressed pulpotomized monkey teeth with freeze-dried bone and Nakashima[57] used dentin matrix to treat amputated pulps of dogs. More recently, crude BMP prepared from bovine bone was used to treat pulpotomized dog teeth.[56,66] The latter studies reported the sequential induction of osteo- and tubular dentin. The preparations of BMP were ill-defined; presumably they included BMP-2, BMP-3, and BMP-7 (OP-1).

Bovine preparations would not be suitable for human teeth. Fortunately, molecular biology techniques can circumvent the necessity of isolating BMP fractions from human bone. Both recombinant human BMP-2 and OP-1 have been purified and characterized,[67,68] and both demonstrated cartilage and bone inductive potential in ectopic sites of rats. And furthermore, hOP-1 has been shown to elicit reparative dentin in exposed pulps of monkey teeth.[69]

The response in this study was dose dependent, a property never before attributed to a pulp agent. The demonstration that reparative dentin can be induced biologically, and its thickness determined by dose, elevates pulp therapy to an altogether new level. Clearly, the regenerative approach to pulp therapy has leapfrogged all other modalities.

We are now entering an era when commercially available recombinant human BMPs will be available for experimentation and clinical trials. A combination of BMPs may be necessary to ensure maximal and predictable reparative dentinogenesis, but these are details to be determined in logical steps. Covey[70] describes the scenario where groups of people can become so involved in hacking through the underbrush that they overlook which jungle they are in. This describes much

of the activity associated with pulpotomy research through the years. But technology has now enabled us to climb a tree and look around. I think that we are in the right jungle at last.

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