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Perspectives on PACS: Where Is Caries Prevention Clinical Research Going?

In this issue, Papas *et al.* (2011) report results of the “Prevention of Adult Caries Study” (PACS). It assessed caries lesion increments among 983 adults in a Phase III randomized controlled trial of the efficacy of 10% (w/v) chlorhexidine diacetate (CH) tooth coating (Prevora[®], CHX Technologies, Toronto, ON, Canada), followed by methacrylate sealant. No difference was observed in net caries increment between individuals receiving treatment and control individuals receiving a placebo. This is disappointing, given the great need for adult caries-preventive methods, encouragement by NIDCR and CDC (Horowitz, 2004; CDC, 2006), and funding by NIDCR. Surely, the authors and *Journal* are to be congratulated for publishing negative findings and avoiding publication bias. The trial confirms the failure of this CH-varnish vehicle in smaller, less rigorous, trials (Banting *et al.*, 2000; Forgie *et al.*, 2000).

Two-layered application of varnish was used “to protect the initial [CH-containing] coating” to increase the contact time between CH and the tooth surface flora while minimizing agent release into saliva; there has been bacteriological support for this (Matthijs and Adriaens, 2002). Long-term, repeated use of antimicrobials and varnish in suppressing nail fungus infection has also not been successful (Murdan, 2002). Prior studies that delivered CH, in various other vehicles, had more positive outcomes (Emilson, 1994), although they lacked the methodological rigor of PACS and other Phase III trials today. Other formulations of CH may yet show value against root-surface caries (Tan *et al.*, 2010). An open-label, non-randomized study of 1% CH gel in head and neck cancer is ongoing (NCT01036412).

Caries prevention research has increased again in the last decade after a long pause, and a few new researchers have joined the search for a remedy. Nevertheless, greater dialogue about how to meet national health goals is needed. Other agents are available but apparently are not being studied energetically, and industry investment and government support are limited, even though the caries problem remains serious and extensive (Rethman *et al.*, 2011). ClinicalTrials.gov lists 137 studies under “dental caries” as of the end of October 2011. Most are not definitive and focus on fluoride varnish, even as evidence indicates that professionally applied topical fluorides are not fully satisfactory in controlling caries, especially in high-risk populations (Weinstein *et al.*, 2009).

Diverse agents with the ability to kill (at least *in vitro*) intact biofilms of prominent species of supragingival bacteria under conditions of concentration, duration, and frequency of exposure superior to CH are known (Tanzer *et al.*, 1977a,b, 1979). There are promising preliminary clinical results for combination treatments where polyvinylpyrrolidone iodine (PVP-I) is applied before fluoride varnish (Milgrom *et al.*, 2011), and strong clinical evidence exists for the effectiveness of diamine silver fluoride to arrest caries

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(Rosenblatt *et al.*, 2009). Strategies involving polyols, particularly xylitol, are also promising (Milgrom *et al.*, 2009a). The Xylitol Adult Caries Study (X-ACT; Bader *et al.*, 2010; NCT00393055), which tested a xylitol lozenge, has been completed, but results have not been released. Results of diverse other strategies aimed at suppressing cariogenic bacteria (Hillman *et al.*, 2000; Tanzer *et al.*, 2010; Shi *et al.*, 2011; Sullivan *et al.*, 2011) have not yet been evaluated in human clinical efficacy trials. Efforts to study the potential of the free dissemination of fluoridated toothpaste among the poor and underserved—especially for very young children—coupled with educational materials that focus on risk and vulnerability and emphasize benefits over risk for fluorides are needed in any case (Milgrom *et al.*, 2009b).

Because resources for trials are scarce, investigators need to focus carefully on populations at high risk. Dental caries is not distributed evenly across the population: PACS sought to be “broadly representative” of the US population and thus included individuals aged 18 to 80 yrs with a rather soft definition of ‘risk’. The study was conducted at four highly diverse sites with, as reported, diverse disease progression rates. Interestingly, PACS excluded the high-risk population with Sjögren’s syndrome, but did not exclude those using anticholinergic-by-intent or -by-side-effect medications. Nonetheless, the investigators did not apparently plan for potentially valuable subgroup analyses of this population (Vollmer *et al.*, 2010).

Interventional studies of caries are expensive, as a result of the chronicity of the disease and the time for lesions to advance to reliable lesion detection levels. They thus require that the duration of studies be adequate not only for the detection of intervention effects, but also for the recruitment of sufficient study participants to withstand losses during follow-up, as well as for the maintenance of trial staff. The duration of the PACS was only 13 mos. PACS also provided filling of cavities before randomization and first treatment, and after 6 mos, reflecting ethical concerns with ignoring lesions. Such an approach necessarily blunts discrimination between treatments, because the best predictor of new tooth decay lesions is existing lesions (Twetman and Fontana, 2009), yet early cavitated (D_2) lesions would have likely advanced minimally during the unusually short 13-month study period (Mejäre *et al.*, 2004).

RECOMMENDATION

The development and validation of new caries prevention strategies for adults—particularly those most vulnerable—should be a priority for the dental profession, industry, and research community. As the US population ages and increasing numbers are affected by xerostomia from pharmaceuticals and systemic disease, this problem will grow worse. Existing preventive and restorative solutions are not completely effective, and many people do not have access to this conventional care. A more concerted effort to clinically evaluate the most promising approaches is needed, but the design of such trials demands much careful discussion and scrutiny from the perspectives of both design and biological vantage points.

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