Paradigm Lost: A Perspective on the Design and Interpretation of Regenerative Endodontic Research

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Abstract

Regenerative endodontic procedures are rapidly gaining the attention of clinicians and investigators alike. However, it is often challenging to understand various regenerative studies and to interpret their results. The present review addresses this problem by focusing on recent strategies for developing standardized clinical protocols, understanding the full spectrum of clinical and translational research and its relationship to selection of proper outcome measures, as well as reviewing the fundamental role of paradigms in designing and interpreting regenerative studies. *(J Endod 2014;40:S65–S69)*

Key Words

Mesenchymal stem cells, pulp biology, regenerative endodontics

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Regenerative endodontic procedures are rapidly gaining the attention of clinicians and investigators alike. Several recent reviews (1–7), including articles published elsewhere in this symposium (8), provide important clinical and biological summaries of regenerative endodontic procedures. This review builds on this prior work by focusing on broader questions of developing standardized clinical protocols, understanding the spectrum of clinical and translational research and how it controls the selection of proper outcome measures, as well as emphasizing the role of paradigms in designing and interpreting regenerative studies.

Development of Standardized Regenerative Clinical Protocols

Many clinicians would agree that the modern era of regenerative endodontics was launched by the case report of Banchs and Trope (9) in 2004. This article prompted the subsequent publication of more than 150 regenerative endodontic cases (4). As recently summarized (4), a range of clinical protocols have been used to treat these cases, with varying irrigants, medicaments, clinical procedures, and follow-up times. This has led to the growing recognition of the need of developing a standardized clinical protocol for regenerative endodontic procedures. However, how can a standardized protocol be developed in the absence of randomized controlled clinical trials?

To address this issue, the American Association of Endodontists (AAE) formed a standing committee on regenerative endodontics in 2007. This committee meets regularly and has developed initiatives for forming an online clinical registry of regenerative cases and developing continuing education materials, new insurance treatment codes, and a standardized clinical protocol, with these materials available via the Internet (10). In developing guidelines for a standardized protocol, the AAE Regenerative Endodontics Committee followed a procedure similar to that used successfully for developing guidelines for prevention of infective endocarditis (11). Although the actual clinical procedures designed to prevent infective endocarditis or to deliver regenerative endodontic procedures are quite different, they share a similar lack of randomized controlled clinical trials and therefore are both based on lower levels of evidence. As illustrated in Table 1, standardized guidelines for both procedures have been developed by using an iterative process of interpreting relevant clinical and preclinical studies, evaluating the strength of the evidence, and forming consensus-driven recommended clinical protocols. This approach has been successfully used worldwide to promulgate guidelines for the prevention of infective endocarditis. Similarly, the most recent revision to the standardized regenerative endodontic protocol was published online in July 2013 and is available for global dissemination (12). Of course, unlike protocols to prevent bacterial endocarditis, regenerative endodontic procedures can be evaluated by randomized controlled trials, and future recommendations are likely to be based on much higher levels of evidence.

In contrast to developing evidence-based guidelines, one published report recommended that the current lower levels of evidence should restrict the use of regenerative procedures to only those cases when all other treatments are not suitable or have failed (13). As practicing clinician scientists, we do not agree with this viewpoint. The failure to provide treatment to children with immature teeth and pulpal necrosis would subject them to long-term functional and esthetic challenges, particularly because many of these cases are maxillary incisors. Moreover, alternative treatments such as extraction

TABLE 1. Procedures for Developing Standardized Clinical Protocols

	Infective endocarditis	Regenerative endodontics
Professional organization	American Heart Association	American Association of Endodontists
Standing committee	Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease	Regenerative Endodontics Committee
Process for developing standardized recommendations	Survey published studies, evaluate level of evidence, reach consensus on recommended guidelines	Survey published studies and AAE clinical registry of cases, evaluate level of evidence, reach consensus on recommended guidelines
Process for revising guidelines	Monitor literature for new findings that require revision to guidelines	Monitor literature for new findings that require revision to guidelines

and placement of dental implants are contraindicated in the child with a rapidly growing craniofacial skeleton. Finally, the continuous publication of an ever-increasing number of regenerative cases suggests that it is possible to save these teeth with satisfactory functional and esthetic outcomes (4). Just as with guidelines to prevent infective endocarditis, the structured development of standardized recommendations for regenerative endodontics provides an evidence-based approach that guides clinicians in providing necessary treatment. Of course, as the field evolves, it is likely that the guidelines will be revised on the basis of the outcomes of higher levels of evidence such as randomized clinical trials. From this perspective, it is important to realize that the premise of level of evidence is to apply the best available evidence in your practice and not to withhold treatment simply because the level of evidence is less than ideal.

Designing and Interpreting Regenerative Endodontic Studies

There is considerable debate on the ideal outcome of regenerative endodontic treatment. Is it complete histologic regeneration of the pulp-dentin complex? Is it continued root development? Is it lack of signs and symptoms of an infection? Is it the patient's satisfaction with treatment? Although there are merits for each of these outcomes, the debate actually misses an important point; all of these outcomes are appropriate, but they answer different questions.

The field of clinical and translational research has evolved considerably during the last 10 years (14–17), leading to a recognized model that depicts the entire spectrum of clinical and translational research (Fig. 1). This spectrum ranges from preclinical studies to human clinical research to clinical practice to population-based studies, and these domains have been characterized as T1, T2, T3, and T4 levels of research. These are not isolated silos of research; instead, knowledge and insight travel both ways across each of these domains. In general, T1 and T2 experiments are conducted with much more control over the experimental conditions than T3 and T4 studies, but with smaller sample sizes. In contrast, T3 and T4 studies generally incorporate much larger sample sizes collected under "real-life" conditions, but with data collected under less controlled experimental designs. For example, the study by Molander et al (18) on one-appointment and two-appointment procedures for nonsurgical root canal treatment is a classic T2-level study that was conducted under highly controlled experimental conditions (including microbial sampling), with well-defined outcome measures but a relatively small sample size ($N = 101$). In contrast, the study by Salehrabi and Rotstein (19) that used an insurance database on endodontic outcomes is a strong T3-level study collected under actual real-life (private practice) conditions, with an enormous sample size ($N > 1.4$ million) but using a relatively loosely defined clinical outcome (survival) that was collected under uncontrolled clinical conditions. It is important to realize that a T2 study is not inherently better or worse than a T3-level study. Instead, these studies have different purposes; a T2 study generates knowledge about the efficacy of clinical interventions applied under optimal highly reproducible conditions, whereas a T3 study provides important knowledge about how interventions work in real-life settings. Both levels of research are important as new knowledge is generated and applied to treating our patients. In addition, T4 research has major population-level or policy-level implications; one dental example is a cost-benefit analysis of water fluoridation on caries.

The organizational model depicted in Figure 1 has direct application to understanding why the "ideal" clinical outcome depends on the experimental question being asked. As a simple example, prior studies

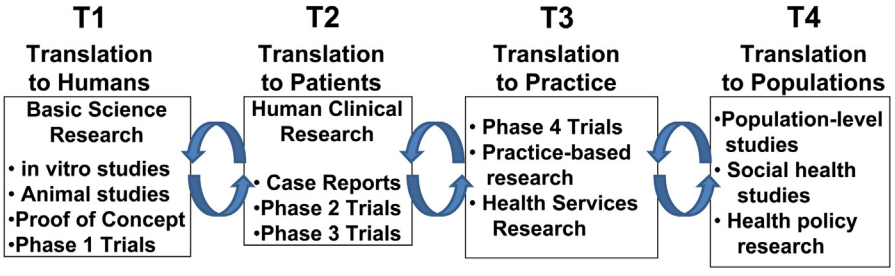

Figure 1. The spectrum of clinical and translational research. There are 4 broad domains of clinical and translational research (T1–T4). These domains serve to translate basic research knowledge into early testing for clinical efficacy or safety (T1), uses highly controlled experimental conditions (eg, a randomized clinical trial design) to evaluate clinical outcomes in patients (T2), studies how guidelines work in actual private practice settings (T3), and determines the impact of interventions on the health of populations (T4).