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From initial case report to randomized clinical trial through 20 years of research in periodontal therapy

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Abstract

Aim: Case reports (CRs) are often the first publication of a new treatment, but randomized clinical trials (RCTs) are needed to confirm the data. The aim of this study was to evaluate how many therapies published as CRs were followed by RCTs of these therapies over a 20-year period.

Material and Methods: Two researchers conducted a search through international periodontal journals and found the CRs on periodontal treatments published from 1984 to 1986. Subsequent electronic searches made it possible to verify how many of the treatments published as CRs were also investigated through RCTs over the following 20 years.

Results: Thirty-one different therapies were selected out of the 33 published CRs; 15 (48%) of these 31 treatments were investigated by RCTs over the next 20 years.

Conclusions: As 52% of the CRs were not validated by RCTs, practitioners should view their results with caution.

Key words: bibliometry; case report; periodontal research; periodontal therapy; randomized clinical trial; Science Citation Index

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Case reports (CRs) are frequently published in health care literature. More than 240,000 CRs appeared in MEDLINE from 1997 to 2002 (Sorinola et al. 2004). CRs are used to propose new treatments or to focus on specific aspects of current therapies (Jenicek 2001). As the aim of the CRs is essentially descriptive, the treatments they propose should be validated by randomized clinical trials (RCTs). In fact, thanks to the use of control groups, randomization and, in general, a more rigorous scientific method, the RCTs are less subject to bias and offer more reliable conclusions.

Different types of bias can affect the conclusions of a CR. One of the most frequent is the positive outcome bias defined as ''the tendency of investigators to submit, or reviewers and editors to accept, manuscripts based on the direction or strength of the study findings'' (Dickersin 1990, Scholey & Harrison 2003). In this regard, a recent study on CRs published in Brazilian dental journals revealed that 99.1% of the CRs had a positive outcome and the procedures were considered and described as successful by the authors (Oliveira & Leles 2006). Such bias leads the reader to think that the results of the treatment are always highly positive.

On the other hand, the CR is often the first publication of a therapeutic concept, the first presentation of a new technique or statement of a biological principle and, therefore, can be considered a breakthrough in scientific evidence (Vandenbroucke 2001). The CR is also an easily readable, understandable scientific article and is generally appreciated by practitioners.

Combining the high sensitivity of CRs with the scientific method of RCTs is a cultural process that takes place when, after some time, an innovative CR is followed by a randomized clinical trial capable of validating its contents. However, in therapy it is not always possible to set up an RCT, for instance in case of rare diseases or due to the high cost of some therapies. In addition, some clinical trials may be of

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scarce interest for the readers and therefore an RCT would not be justified.

A recent study of CRs of medical treatments published in the *Lancet* from January 1996 to June 1997 revealed that over the next 5 years only 11 (17%) of 64 CRs had been followed by controlled clinical studies (Albrecht et al. 2005). No similar study of periodontal literature had been conducted up to the present.

The aim of this study was to seek out the CRs on periodontal treatments published in four accredited international journals between 1984 and 1986 and to ascertain how many of them had then been investigated by RCTs over the following 20 years.

Material and Methods

Three searches were conducted to select articles:

(1) The first one was a hand-search to find the CRs published in four international journals: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *International Journal of Periodontics and Restorative Dentistry* and *Journal of Periodontal Research*. Two researchers (U.P., J.B.) independently conducted the search of articles published from January 1984 through December 1986; in vitro and animal studies were excluded. Then, joined by a third researcher (M.N.) they evaluated the selected CRs and chose only those CRs that dealt with periodontal treatments (gingivitis and periodontitis) of one to five patients. CRs concerning rare diseases were also excluded during this phase because an RCT could not be performed. A condition was considered rare or unusual by definition of the authors of the CR.

(2) Next, the same three researchers (U.P., J.B., M.N.) conducted independent electronic searches to find the RCTs that evaluated one of the treatments described in the selected CRs. The electronic searches covered all the publications referenced through 30 September 2006 in MEDLINE (by PubMed), and the databases of The Cochrane Collaboration (in particular the Cochrane Database of Systematic Review and the Cochrane Central Register of Controlled Trials) and the Institute for Scientific Information (ISI) (in particular, the Science Citation Index Expanded).

The electronic searches in PubMed and in the Cochrane Collaboration database was performed using numerous *key words*, *MeSH terms* and *limits*. Each examiner was free to change the search query in order to obtain as much information as possible and increase the sensitivity of the search. For each of the selected therapies, at least two different electronic searches were performed by each examiner.

The search in the Science Citation Index Expanded was performed verifying each article that cited the selected CRs.

When RCTs were not identified, the search was repeated in order to reduce the probability of false negatives.

(3) Finally, a third, independent electronic search of the Science Citation Index (ISI), by two researchers (M.N., J.B.), yielded the citations from the individual CRs up through 30 September 2006.

Results

After excluding the CRs that dealt with animal and in vitro studies, the paper search yielded 66 CRs. Thirty-three of these were then excluded: eight covered rare diseases, six did not deal with periodontal treatments, nine did not discuss treatments and the 10 that reported on more than five patients were considered case series and hence ''ineligible'' for this study (Fig. 1). The final list comprised 33 CRs concerning 31 treatments (Table 1).

The authors' names, journals, number of citations found, the type of therapy described and the eventuality of corresponding RCTs found are shown in Table 1.

Nineteen CRs were published in the *Journal of Periodontology*, two in the *Journal of Clinical Periodontology*, 12 in the *International Journal of Periodontics and Restorative Dentistry*; none were published in the *Journal of Periodontal Research*.

Several therapies described by selected CRs dealt with mucogingival surgery (nine), some covered surgical treatment of infrabony defects (seven), and 15 dealt with various techniques. The total number of electronic searches was over 300. The electronic searches revealed that 15 (48%) treatments were investigated by RCTs, whereas there were no randomized trials on record for 16 (52%).

The number of citations from the CRs ranges from 0 to 193. The CRs on treatments also investigated by RCT have from 0 to 193 citations; and the CRs on treatments that were not the subject of RCTs yielded from 0 to 31 citations.

Discussion

Up to now, in periodontology, the number of CRs that have been followed by RCTs is unknown. The aim of this study was to determine the percentage of treatments published in CRs that were followed by RCTs over a 20-year period.

The hand-search by the two independent researchers was only conducted to find CRs in the main international periodontal journals between 1984 and 1986. All the journals without peer review systems and those that are not listed by the Institute for Scientific Information were excluded. The 3-year period between 1984 and 1986 was selected to offer a sufficiently long period (20 years) to conduct RCTs after the treatments had been presented as CRs.

After careful evaluation, the researchers excluded 33 of the 66 CRs they had

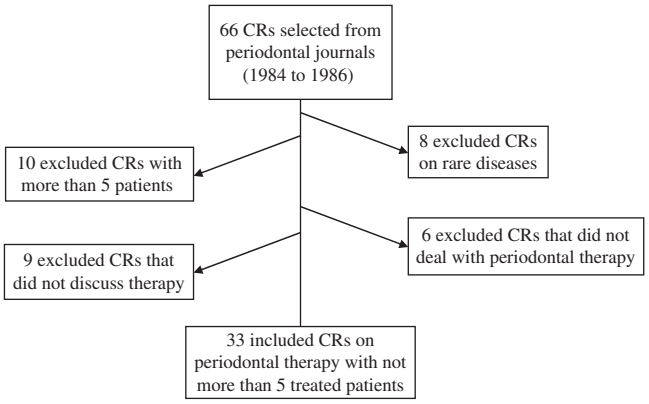

Fig 1. Reasons for the exclusion of case reports (CRs) from this study.

Table 1. Thirty-three selected articles and 31 topics

Article	SCI	Journal	Topic	RCT
Sapkos (1986)*	25	JP	Hydroxylapatite/supracrestal defects	No
			Hydroxyapatite/infrabony defects	
Shepard et al. (1986)	7	IJPRD		
Kenney et al. (1986)	84	JP		Yes
Meffert et al. (1986)	7	IJPRD		
Ellinger et al. (1986)*	28	IJPRD	Biphasic calcium phosphate/infrabony defects	Yes
Tarnow (1986)	34	JP	Semilunar coronally repositioned flap/recessions	Yes
Van Oosten et al. (1986)	5	JP	Amoxicillin/periodontitis	Yes
Moskow (1986)	11	JP	Tetracycline/periodontitis	Yes
Jaffin et al. (1984)	4	JP		
Agudio et al. (1985)	4	IJPRD	Mucointerceptive therapy	Yes
Langer & Langer (1985)	193	JP	Connective tissue graft/recession	Yes
Becker & Becker (1986)	5	IJPRD		
Pollack (1984b)	2	JP	Free gingival graft	Yes
Rostock et al. (1986)	93	JP	Gingivectomy following hyperplasia	Yes
Baldock et al. (1985)	39	JP	Tricalcium phosphate/infrabony defects	Yes
Stahl & Froum (1986)	39	JP		
Bowers et al. (1986)	30	JP		
Mattout & Roche (1984)*	4	JCP	Autogenous bone graft/intrabony defects	Yes
			Autogenous bone graft/furcations	Yes
Miller & Binkley (1986)*	3	JP	Coronally positioned free gingival graft in class 4 recessions	No
			Citric acid/recessions	Yes
O'Leary et al. (1984)*	0	JP	Modified curette/scaling and root planing	Yes
			Modified Orban knife	No
Pollack (1984a)	0	IJPRD	Gingival curettage/periodontitis	Yes
Wagenberg et al. (1986)*	0	IJPRD	Orthodontic extrusion/infrabony defects	No
			Derotation of inclined tooth with infrabony defect	No
Langer et al. (1986)	1	IJPRD	Frozen autogenous bone/infrabony defects	No
Khouri (1986)	1	JP	Orthodontic disinclusion of included teeth	No
Cho & Charbeneau (1986)	1	JP	Freeze dried dura mater grafts/recessions	No
Shapiro (1985)	17	IJPRD	Periodical Curettage/papillae regeneration	No
DiFebo et al. (1985)	6	IJPRD	Combined intraoperative tooth preparation	No
Dello Russo (1985)	10	IJPRD	Immediate surgery/periodontal abscess	No
Greenstein et al. (1985)	5	JP	Hydroxyapatite/ridge augmentation	No
Takei et al. (1985)	31	JP	Papilla preservation with graft	No
Haskell (1984)	1	IJPRD	Rizectomy of a vital tooth	No
Manor et al. (1984)	9	JCP	Teeth spontaneous repositioning/perio surgery	No
Newell & Brunsvold (1985)	0	JP	Modified suturing technique	No

Article: the reference to case reports included in this study; SCI: the number of citations received by each case report calculated with the Science Citation Index; Journal: the journal in which each case report was published; Topic: the main topic discussed; RCT: whether the case report was followed by at least one randomized clinical trial or none.

JP, Journal of Periodontology; IJPRD, International Journal of Periodontology and Restorative Dentistry; JCP, Journal of Clinical Periodontology.

*Sapkos (1986), Ellinger et al. (1986), Mattout & Roche (1984), Miller & Blinkey (1986), O'Leary et al. (1984) and Wagenberg et al. (1986) considered two therapies.

found. There were various reasons for exclusion. Eight CRs described treatments of rare conditions. For example, some rare syndromes were discarded such as Papillon–Lefevre syndrome (Tinanoff et al. 1986) or Gingival Hyperplasia in a patient with arthrogryposis multiplex congenital (Sakamoto et al. 1985). The very limited number of patients affected by these rare disease would not permit the set-up of more complex studies (RCT) and including them in this survey would have produced a bias reducing the percentage of CRs followed by RCTs.

The other excluded CRs did not deal with periodontal disease, and the reports with more than five patients were eliminated because they are, in fact, case series and not CRs. An article was considered as a CR when it reported up to five clinical cases, because in this situation, the interventions are generally presented as clinical cases without the objective of aggregating the results and without the attempt to investigate the variability of the results. Therefore, the aim was to consider as eligible only the articles at the lowest levels of the grading system.

The analysis of the results shows that nearly 50% of the treatments presented as CRs were also investigated by RCTs. This percentage differs when compared with data from other branches of medicine. For example, Albrecht et al. (2005) found that only 17% of the CRs published in the *Lancet* were followed by controlled studies. However, we must note that Albrecht's study also considered CRs on rare diseases and that a much shorter time period, 5 years, was allowed for the conduction of the RCTs.

An important aspect to take into consideration is the expectation of an RCT performed after a CR. In other words, is it always worthwhile waiting for RCTs of therapies suggested by previous CRs? In case of rare diseases, but also in case of some common clinical situations, it is

quite impossible to perform an RCT. In fact, it would only be expected that CRs suggesting a significant periodontal health benefit would be followed by investment in an RCT. In this revision, no attempts were made to weigh the clinical impact of the CRs and this may be considered as a limit of this study.

Over 50% of the treatments discussed in the CRs were not investigated by RCTs over the next 20 years. Many of these treatments are still used today in spite of the lack of scientific evidence. For example, periodic curettage for the re-generation of interdental papillae (Shapiro 1985) has not been studied in an RCT even though the procedure continues to arouse interest and is cited frequently as the data in the Science Citation Index show (Table 1).

The CRs analysed in the present study obtained a highly variable number of citations ranging from zero for some to a maximum of 193 for the CR that presented the connective tissue graft technique for treating gingival recession (Langer & Langer 1985). The fact that some CRs obtain a high number of citations should not be surprising. In fact, a recent publication has shown that, paradoxically, the studies that do not include control groups are cited more frequently than controlled and randomized trials (Nieri et al. 2007).

Considering the descriptive nature of CRs and their low position in terms of grading scientific reliability, new treatment proposals should, insofar as possible, be followed by RCTs to prove their validity. In fact, this type of study may prove ineffective or even dangerous and should not be accepted without careful scientific evaluation. One typical example is the CR published by Nyman et al. (1982) that was the first to discuss the clinical concepts of periodontal regeneration and described the use of non-resorbable membrane. The subsequent RCTs confirmed the validity of this approach in the treatment of infrabony defects (Cortellini et al. 1998, Needleman et al. 2006). In this case, the therapy first proposed in the CR proved effective.

One interesting question that can arise is the following: Were the results of the 15 therapies presented as case studies and then analysed by RCTs scientifically validated?

For instance, the connective tissue graft technique first described by Langer & Langer in 1985 for treating gingival recessions in four patients revealed optimal results in terms of root coverage. Successively, several systematic reviews of RCTs (Roccuzzo et al. 2002, Clauser et al. 2003, Oates et al. 2003, Cairo et al. 2008) have definitively proved that this procedure is effective in the treatment of Miller's Class 1 and 2 gingival recession defects and can be considered one of the preferred treatments.

On the contrary, the use of citric acid in the chemical treatment of root coverage proposed by Miller & Binkley (1986) was subsequently found to be ineffective and useless for obtaining greater root coverage (Roccuzzo et al. 2002).

In addition, there are also cases, such as the use of autogenous bone grafts for infrabony defects, where the CRs were followed by RCTs which did not yield clearly unambiguous results making it impossible to draw any certain conclusions (Nery et al. 1990, Yukna 1994, Trombelli et al. 2002, Reynolds et al. 2003).

A more detailed analysis of the validation of periodontal treatments presented as CRs in 1984–1986 and investigated by RCTs will be the topic of another paper. In this future study, the number, the quality and the conclusions of the same RCTs will be presented.

To conclude, if, CRs are undoubtedly attractive for authors because of their simple structure and immediate results and for practitioners because of their ready comprehensibility and interpretation with respect to RCTs, then CRs can often present severe bias that may lead to interpretational errors which can be prevented by more reliable studies such as RCTs. The fact that only half of the CRs were followed by RCTs and that they were conducted several years after the publication of the first CR, means that great caution should be exercised when considering the therapeutic indications described only in CRs.

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Clinical Relevance

Scientific rationale for the study: The CR is useful for proposing and describing a new therapy. However, the CRs can often present considerable bias that may lead to fundamental interpretative errors. More reliable studies, such as the RCTs, are needed to offset the inherent risks of the CRs.
Principal findings: In periodontology, less than half the therapies described in CRs were followed by RCTs within the 20 years following publication.
Practical implications: The therapeutic indications obtained from CRs alone must be viewed with considerable caution.