Assessment of Bias in Methodology for Randomized Controlled Trials Published on Implant Dentistry

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Purpose: **The purpose of this study was to assess randomized controlled trials (RCTs) published on implant dentistry over a 10-year period (1991 to 2000), based on the reporting of control of potential sources of bias in the design methodology.**

Materials and Methods: **A MEDLINE search was conducted for RCTs using keywords *dental implant* and publication type *randomized controlled trial*. Three areas of trial methodology were assessed: (1) adequate reporting of randomization procedure, (2) blinding in assessment of outcomes, and (3) handling of subject withdrawals in data analysis. A score of 1 or 0 was assigned for each of the three potential sources of bias. Thus, the maximum quality score for an RCT is 3 and the minimum is 0.**

Results: **Forty-three articles met criteria for classification as RCTs. Method of randomization was explicit in 51% of the RCTs, but only 12% incorporated blinding in the assessment of outcome. Ninety-eight percent accounted for all subjects at the end of the study. Looking at overall quality scores, only 2% of RCTs adequately reported on control of bias in the three areas examined, 56% were deficient in one area, and 42% were deficient in two areas.**

Conclusion: **Reporting of randomization procedures and blinding in outcomes assessment for most implant RCTs was inadequate. Subject retention and documentation of subject withdrawals were adequately reported.**

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INDEX WORDS: MEDLINE, study design, clinical trial, RCTs, prosthodontics, osseointegrated implants

THE DISCOVERY and subsequent development of osseointegration represents one of the most significant advances in dentistry, expanding dentists' ability to offer definitive tooth replacement to patients with missing teeth. The serendipitous discovery of titanium implants has been followed by systematic scientific inquiry including molecular, cellular, laboratory, and animal research, as well as human clinical trials. The randomized controlled trial (RCT) is the most valid research design for evaluating treatment interventions. Conclusions about efficacy of treatment derived from nonexperimental approaches often overestimate treatment effect. In medicine, confirmation of the efficacy of many treatments and the uselessness or harmfulness

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of others have been made through RCTs.[1] An RCT is any planned experiment or investigation in which assignment of subjects to treatment groups is by random allocation. The process of randomization of subjects to different treatment groups provides the best available method for providing homogeneous study populations, thereby minimizing bias in the allocation of subjects to specific treatments.

The quality of clinical trial methodology depends on several features of the study design, including the method used for randomization, criteria for subject selection, description of intervention, blinding procedures, treatment of data, and statistical analyses.[2] Bias is "any trend in the choice of a sample, the making of measurements on it, the analysis and publication of findings that tend to give or communicate an answer that differs systematically from the true answer," and can occur in different phases of the trial methodology.[3] Three dimensions of trial methodology that are important sources of bias include the quality of allocation of subjects to treatment groups (control of bias at entry), the extent to which subjects and/or investigators are kept unaware of the group assignment of subjects (control of bias in assessment of outcome), and the extent to which subjects are included in data analysis (control of bias after entry).[4]

An assessment of RCTs published in prosthodontic journals over a 10-year period revealed inadequacies in reporting control of potential sources of bias in trial methodology.[5] Out of 62 reviewed prosthodontic RCTs that stated random allocation of subjects to treatment groups, only 47% explicitly described the method used for randomization. The others simply stated that patients were randomly assigned, thereby not providing sufficient information for the reader to judge the rigor with which assignment bias was addressed. Blinding in outcomes assessment was reported in only 40% of these RCTs. This low percentage was attributed to practical problems in clinical prosthodontic research where blinding is often not possible. When the authors reviewed the nature of treatment in the RCTs that did not incorporate blinding, they determined that only 19% of those could have incorporated blinding in the assessment of outcome. Blinding of either investigators or subjects was not appropriate in 40% of the RCTs because of the nature of the treatment intervention. Seventy-six percent of prosthodontic RCTs reported the reasons for subject attrition, making this potential source of bias the most well-controlled. Overall quality scores for prosthodontic RCTs reviewed in this study revealed that only 16% attempted to control bias in the three areas examined. Forty percent were deficient in one area, 34% were deficient in two areas, and 10% were deficient in all areas examined.

The purpose of this study was to assess RCTs published on implant dentistry based on the reporting of control of potential sources of bias in the design methodology.

Methods

A MEDLINE search was conducted for RCTs published on implant dentistry using keywords *dental implant* and publication type *randomized controlled trial*.[6] The search was limited to English language articles published between 1991 and 2000. A trial was considered an RCT if it met the following criteria: (1) it involved human subjects, (2) it included at least two treatment groups, and (3) it stated that subjects were randomly allocated to treatment groups.

Two calibrated reviewers independently reviewed the methodology of each RCT in three areas using a scheme developed through the Cochrane Collaboration.[4] The three dimensions of trial methodology assessed were control of bias at entry, control of bias in the assessment of outcome, and control of bias after entry. A score of 1 or 0 was assigned to each of the three potential sources of bias. In evaluating control of bias at entry, the treatment allocation procedure was evaluated to ensure that investigators were not able to predict or influence which treatment the patients would receive in the study. A score of 1 was given if the method of randomization was explicitly reported. In evaluating control of bias in outcomes assessment, the assessment procedure was evaluated on whether it ensured that either investigator or subject had no knowledge of treatment allocation. Reporting of investigator and subject blinding (double-blind), investigator or subject blinding (single-blind), or no blinding was noted. A score of 1 was given when either single- or double-blinding was reported. In evaluating control of bias after entry, it was noted whether subjects were lost to follow-up and if so, whether the reason for attrition was reported. A score of 1 was given if the number of subjects was the same throughout the study or when reasons for subject dropouts were reported.

Thus, the maximum quality score for each RCT was 3 (good bias control), and the minimum was 0 (poor bias control). A third calibrated reviewer scored the trial methodology if there was disagreement between two reviewers. Agreement between at least two

reviewers established the final score. Disagreements were few and involved mostly the decision of whether the randomization procedure was explicitly described. In all instances, discussion among the three reviewers resulted in agreement. Frequencies were calculated for each dimension of trial methodology and the overall quality scores.

Results

Seventy articles were retrieved from MEDLINE, of which 67 were available at the Baylor Health Sciences Library for review. It is not believed that retrieving the three additional articles would alter the results of this study. The 67 articles were published in 16 different journals. Forty-three articles (64%) met inclusion criteria for classification as RCTs.[7-49] *Clinical Oral Implants Research* published most of the RCTs (23%), followed by *International Journal of Oral and Maxillofacial Implants* (12%), *Journal of Prosthetic Dentistry* (12%), *International Journal of Oral and Maxillofacial Surgery* (9%), and *Journal of Dental Research* (9%). Table 1 presents the results of the MEDLINE search according to journal source.

Table 1. Journal Distribution of Implant RCTs

	RCT	
Journal	*Yes*	*No*
British Journal of Oral and Maxillofacial Surgery	1	
Clinical Implant Dentistry and Related Research	1	
Clinical Oral Implants Research	10	
Community Dentistry and Oral Epidemiology	1	
Implant Dentistry	2	4
International Journal of Oral and Maxillofacial Implants	5	5
International Journal of Oral and Maxillofacial Surgery	4	
International Journal of Prosthodontics	2	
Journal of Clinical Periodontology	1	
Journal of Dental Research	4	
Journal of Oral and Maxillofacial Surgery		9
Journal of Oral Rehabilitation	2	
Journal of Periodontology	2	3
Journal of Prosthetic Dentistry	5	1
Journal of the American Dental Association	1	
Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics	2	
Total	43	24

Table 2. Control of Bias in RCTs

Potential Source of Bias	*RCTs N = 43*
1. At entry	
Method of randomization was reported	22 (51%)
2. Assessment of outcome	
Blinding was performed and reported	5 (12%)
3. After entry	
All subjects accounted for at the end of the study	42 (98%)

Method of randomization was explicit in 51% of the RCTs; however, only 12% incorporated blinding in the assessment of outcome. Ninety-eight percent of RCTs accounted for all subjects at the end of the study. Looking at overall quality scores, only 2% of RCTs attempted to control bias in the three areas examined, 56% were deficient in one area, and 42% were deficient in two areas. Tables 2 and 3 summarize the result of the quality assessment.

Discussion

Evaluating treatment effectiveness often involves searching published evidence. MEDLINE is an electronic biomedical research literature database that includes literature from the allied health fields, biological and physical sciences, humanities, and information science as it relates to medicine and healthcare. MEDLINE contains information indexed from approximately 3900 journals published from 1966 onward, and provides easy access to published evidence; however, it has been shown that experts can find only about half of the RCTs documented in MEDLINE, whereas an experienced clinical searcher will find only half the RCTs the expert searcher can find.[50] Manual searching of journals for RCTs is an effective but time-consuming search strategy. In a study of MEDLINE search strategies for detecting RCTs published in prosthodontic journals, the tested strategies that provided the best balance between sensitivity and precision were searches by publication type *clinical trial* and publication type *randomized controlled trial*.[6] However, MEDLINE only started using publication type *randomized controlled trial* as an indexing category in 1991.[51]

Table 3. Frequency of Studies Scored According to Source of Bias

No. of Studies N = 43	*At Entry*	*Assessment of Outcome*	*After Entry*	*Overall Score*	*Reference List*
0	0	0	0	0	–
17	0	0	1	1	9, 11, 15, 16, 18, 19, 21, 24, 25, 32, 33, 35, 41, 42, 45–47
0	0	1	0	1	–
1	1	0	0	1	12
0	1	1	0	2	–
20	1	0	1	2	7, 8, 10, 13, 14, 17, 20, 23, 26–31, 34, 36, 38, 40, 48, 49
4	0	1	1	2	22, 39, 43, 44
1	1	1	1	3	37

Adequate reporting of trial methodology facilitates interpretation of trial design and results, allows for comparison with other trials, and permits replication of the trial. In this study, we considered three dimensions of trial methodology that are potential sources of bias. The first was randomization. Randomization establishes the basis for testing statistical significance by ensuring that baseline subject characteristics which might confound an observed association are distributed equally, except for chance variation, among the randomized groups. Because randomization is the cornerstone of an RCT, it is important that it be done correctly and reported adequately. Method of randomization was explicit in 51% of implant RCTs. Randomization methods used included balanced allocation or stratification (41%), computer randomization software (27%), lots (14%), blocks (4%), table of random numbers (4%), and quasi-random methods such as sequential or alternate assignments (9%).

Forty-nine percent of the RCTs simply stated that patients were assigned randomly. If an RCT reports random assignment of patients without describing the method used for randomization, the elimination of bias in patient assignment remains unresolved. Not following a pre-established randomization protocol does not necessarily mean that baseline characteristics of interest might not be equally distributed among the groups. However, not using a randomization protocol results in a greater risk of introducing bias in the assignment of subjects to a particular treatment group, intentional or not, in a way that could favor one treatment over another based on existing patient characteristics. In the hierarchy of patient assignment to treatment groups, not using a randomization protocol carries a greater risk in introducing bias than doing a formal randomization procedure or a quasi-random method that involves sequential or alternate assignment. Although quasi-randomization does not have the rigor of formal randomization, it still provides a means for reducing bias by eliminating the possibility of the investigator influencing patient assignment. Following a randomization protocol is a means of eliminating possible bias by averaging extraneous variables; it allows valid comparison of treatments. RCTs should aim to adequately describe the method of randomization used in allocating patients to treatments.

Randomization eliminates the influence of confounding variables that are present at the time of randomization. It does not affect confounding variables that may develop during the period of the study or follow-up.[52] To control for bias in assessing outcome variables, a study should be designed such that neither investigators nor subjects have knowledge of treatment allocation. In the implant RCTs reviewed, blinding of investigators and/or subjects to treatment allocation was performed in only five (12%) of the studies, making this area the most poorly controlled among the three potential sources of bias. In three of the RCTs, the investigator performing outcomes assessment was blinded to group assignment of subjects. Both investigator and subject were blinded in two of the RCTs. Double-blinding was possible in these two RCTs since the intervention allowed this design (antiseptic mouthrinse vs. placebo and medication vs. placebo)[37,39]. Thirty-eight of the 43 RCTs did not incorporate blinding in outcomes assessment. After reviewing the nature of treatment in the RCTs that did not perform or report blinding, it was judged that only 10 of the 38 RCTs (26%) could have incorporated blinding in outcomes assessment. Blinding may be difficult or impossible to achieve in the design of implant clinical studies if

the intervention is obvious and cannot be masked from the investigator performing the measurements. For instance, it would not be feasible to blind the investigator in an RCT comparing soft tissue parameters between implants with ball versus bar attachments,[13] because the intervention is obvious.

Handling of subject dropouts and withdrawals is important in data analysis. In this study, a score of 1 was given if the study reported no subject dropouts or withdrawals, or when reasons for subject dropouts or withdrawals were reported.

The type of research question being asked in an RCT determines in part the appropriate duration for the study to detect the outcome of interest. For instance, an RCT comparing chewing efficiency between fixed and removable implant-supported prostheses will require a shorter study period than one comparing bone-loss around implants supporting either type of restoration. The longer the duration of a study, the greater the risk for subject attrition, since subjects may move, die, lose interest in continued participation, or withdraw for various other reasons.

Describing subject dropouts or withdrawals is important, since adequate reporting allows the reader to judge whether the reasons for dropout or withdrawal were study-related. For instance, in a study comparing patient satisfaction between two treatment modalities, a patient may drop out because the assigned treatment was unsatisfactory. If the patient did not report the reason for the withdrawal, the investigator may simply count the subject as a dropout and not a treatment failure. In these types of studies, it may be appropriate to present statistical results that count withdrawals as treatment failures. In the implant RCTs reviewed, 98% accounted for all subjects at the end of the study, making this potential source of bias the best controlled of the three.

Comparing these results with data from general prosthodontic RCTs,[5] implant RCTs had better control of bias at entry (51% vs. 47%) and after entry (98% vs. 76%), while control of bias in assessment of outcome was poorer (12% vs. 40%). The low percentage of blinding in the assessment of outcome reflects practical problems inherent in the type of intervention evaluated. All papers that met inclusion criteria for the "prosthodontic review"[5] and this study were included regardless of duplication ("double dipping") of some papers in the review. In the "prosthodontic review,"[5] 15% of the RCTs involved implants in their subject area.

Conclusion

Reporting of randomization procedures and blinding in outcomes assessment for most implant RCTs was inadequate. Subject retention and documentation of subject withdrawals were adequately reported.

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