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Review Article

Risk of bias of animal studies on regenerative procedures for periodontal and peri-implant bone defects – a systematic review

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Abstract

Objectives: (1) To assess the risk of bias of studies in which animal models were used for investigating regenerative therapies for periodontal and peri-implant defects. (2) To investigate changes in risk of bias by comparing samples drawn from two different publication periods.

Material & Methods: We searched the PubMed and LILACS electronic databases, independently and in duplicate, for randomized and controlled trials published from 1998 to 2000 and from 2008 to 2010. Hand searching included search of 10 dental journals, in the issues published between August 2008 and August 2010. Studies on non-human primates and canines were included. We assessed independently and in triplicate the risk of bias with reference to a six-item checklist based on the Cochrane Collaboration's tool for assessing the risk of bias and information about formal sample size calculation.

Results: One hundred and seven studies were included in the review. Checklist items were poorly reported in the studies selected, and therefore for most of the studies, the risk of bias was unclear.

Conclusion: As a result of the unclear risk of bias of animal studies in periodontal and peri-implant treatments, it is difficult to determine the accuracy of treatment effect estimates. There is a need for standardization of reporting procedures on animal experiments.

Key words: animal research; controlled trial; ethics; methodological quality; randomised controlled trial; risk of bias

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Conflict of interest and source of funding statement

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Animal models are important in planning and conducting clinical trials in dentistry. The rationale is that potentially dangerous or ineffective therapy can be avoided if clinical safety can be demonstrated for animals before transfer to humans. To be justifiable, however, animal experiments should be rigorously conducted to avoid or reduce any bias that can interfere with the conclusions

drawn from the results. Results from studies on animals that do not use randomization and blinding are more likely to report a difference between study groups than studies that use these methods (Bebarta et al. 2003). Even better designs, for example randomized controlled trials (RCTs), can also lead to problems – because RCTs with small sample sizes may have low power to detect differences between groups, they might furnish misleading results. For these reasons, it is imperative that the methodology used in clinical trials based on experiments with animals is as rigorous as that applied to humans.

To enable other researchers to replicate the results of a study, and to enable systematic comparison of efficacy among studies, researchers should provide explicit information on how the study was performed (Perel et al. 2007, Faggion et al. 2009). In this way, the body of evidence can be assessed in its entirety to provide guidance for future research.

Systematic reviews of animal studies in dentistry normally do not consistently assess the risk of bias of included studies (Faggion et al. 2011). Many different animal species have been employed in pre-clinical trials regarding periodontal and peri-implant tissue regeneration. In terms of compositional and microstructural properties, monkeys and dogs are considered to be the most similar creatures to humans (Wang et al. 1998, Pearce et al. 2007). Moreover, it is believed that anatomical and defect size characteristics of large animals such as monkeys and dogs are more similar to those of humans than the respective characteristics of small animals (Pellegrini et al. 2009). Large-animal models are therefore preferred by regulatory bodies for demonstration of the safety and efficacy of therapies or new products (Pellegrini et al. 2009).

The aim of the present work was to assess the risk of bias of studies on regenerative procedures for periodontal and peri-implant bone defects in which monkeys and dogs were used as animal models. In addition, the present work investigated changes in risk of bias as observed by comparing two different publication periods.

Material and Methods

Focused question

Which level of risk of bias exists in animal studies that include monkeys and dogs as test subjects for periodontal and peri-implant regenerative procedures?

Literature search

An extensive search of the PubMed and LILACS databases was conducted to retrieve literature published from 31st August 2008 up to 31st August 2010. Searches were conducted with the key words: ((dog* or monkey* or baboon*) AND periodont* AND regenerat* AND defect*), ((dog* or monkey* or baboon*) AND (peri-implant* or perimplant*) AND regenerat* AND defect*), (canine AND model AND (peri-implant* or perimplant*)), (non-human primate* AND periodont* AND defect*), (non-human primate* AND (peri-implant* or perimplant*) AND defect*), (emdogain or enamel matrix derivative) AND (dog* or non-human primate*), (non-human primate or canine) AND socket AND preservation, (non-human primate or canine) AND ridge AND augmentation. All key word terms were combined with a Boolean logic strategy ("OR"). The reference lists of the papers included were also searched manually to retrieve potential studies. We used the internet search engine "Google Scholar" in English, French, German, Italian, Portuguese and Spanish to retrieve articles published in the language of the original search engine (for example, articles in Italian in Google Italy, articles in German in Google Germany, etc.). Hand searching included a complete search of: the Journal of Clinical Periodontology; Clinical Oral Implants Research; Clinical Implant Dentistry and Related Research; the Journal of Periodontology; Clinical Oral Investigations; Journal of Periodontal Research; Implant Dentistry; Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics; the International Journal of Periodontics and Restorative Dentistry and the Journal of Oral Implantology, in the issues published between August 2008 and August 2010. Finally, grey literature was searched in OpenGrey – System for Information on Grey Literature in Europe (http://opengrey.eu/). All literature searches were performed independently and in duplicate by two reviewers (C. M. F. and N. N. G.).

Screening and data abstraction

Two reviewers (C. M. F. and N. N. G.) screened independently and in duplicate titles and abstracts of articles for possible inclusion in the study. The full text of RCTs conducted on animals was obtained for further quality assessment. Any disagreements in study selection were resolved by consensus. Methodological characteristics comprising risk of bias of included studies were abstracted independently and in duplicate into standardized tables by two reviewers (C. M. F. and N. N. G.).

Inclusion/exclusion criteria

We considered RCTs and controlled trials on therapy for regeneration of periodontal and peri-implant bone defects tested in dog and monkey models. Regenerative procedures had to be performed in the oral cavity of the animals tested, simulating guided tissue or bone regeneration in humans. Extraction socket and vertical ridge augmentation were regarded as periodontal and peri-implant bone defects and were therefore also included. Studies using monkeys and dogs were selected because these animals appear to be most representative regarding periodontal regeneration (Sculean et al. 2008) and to have properties most similar to humans (Wang et al. 1998, Pearce et al. 2007).

Studies that included only implants with modified surfaces or surfaces coated with materials (but without any extra regenerative material or membrane), in vitro studies, and studies dealing with animals other than non-human primates and dogs were excluded from this study. Other types of study design (e.g. case reports, case series and reviews) were also excluded from this study.

Risk of bias assessment

We assessed the risk of bias of RCTs and controlled trials using some of the components of the Cochrane Col-

laboration's tool for assessing risk of bias. Moreover, reporting of sample size calculation was assessed as a further methodological criterion for precision of results. The Cochrane tool is a domain-based evaluation that assesses different types of bias, for example selection, performance, attrition and detection (Higgins & Altman 2009).

We compared sections of the included studies directly by means of the proposed assessment tool. To judge the risk of bias in the studies, we used the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.2 (section 8.5.3, table 8.5.c). If the criteria proposed in tables 1 and 3 of that handbook were met, we assigned the answer YES (i.e., the risk of bias was low). In contrast, if the criteria were not met, we assigned the answer NO, indicating a high risk of bias. If there was insufficient information or the study did not address the required criteria, neither the answer YES nor the answer NO could be assigned. Instead, the answer UNCLEAR was awarded to such studies (i.e., the risk of bias was uncertain).

This assessment of the methodology of the RCTs included was performed independently in triplicate by all authors, and any disagreements in the assessment were resolved by consensus. Review Manager Software (RevMan Version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration 2011) was used to generate risk of bias graphics.

Comparison of study samples

We selected a second sample of studies published between 31st August 1998 up to 31st August 2000 from the PubMed database. We again assessed independently and in triplicate, the quality of reporting of this second sample. We then graphically compared the risk of bias for both samples. Again, any disagreements in the assessment were resolved by consensus.

Results

Selection of the studies

In the first sample of studies (from 2008 to 2010), we initially retrieved 124 titles. After full-text assessment and consensus between reviewers, 65 papers were included. In the second sample of studies (from 1998 to 2000) we initially retrieved 61 potential manuscripts. Forty-two papers were selected for assessment of risk of bias. In total, one hundred and seven papers were therefore included in the review. The level of inter-reviewer agreement was 75%. Figures 1 and 2 depict the detailed literature search process and the reasons for exclusion of studies. The list of included studies is reported in the references [S6, (Appendix, Supporting information)]. The characteristics of the included studies are reported in Tables S3 and S5 (Appendix, Supporting information).

Risk of bias

Of the 749 items assessed for 107 papers (i.e. seven items for each paper), 581 (78%) were at unclear risk of bias. Domains related to the randomization process were almost never reported. Allocation concealment method and adequate sequence generation were never reported in the sample of studies published from 1998 to 2000. In the 2008–2010 sample, allocation concealment method and adequate sequence generation were reported once (1.5% of the sample) and ten times (15% of the sample) respectively. Blinding of caregivers was never reported in the sample of 1998–2000, whereas in the other sample, this topic was reported only once (1.5% of the sample). Examiner blinding was reported five times (12% of the sample) and 17 times (26% of the sample) in the 1998–2000 and 2008–2010 samples respectively. Only one study in the two samples reported to have performed sample size/statistical power calculation. The complete entries for studies domains are reported in Tables S2 and S4, Appendix (Supporting information).

Figures 3 and 4 illustrate, graphically, differences between results from assessment of the methodology of studies published from 1998 to 2000 and those published from 2008 to 2010.

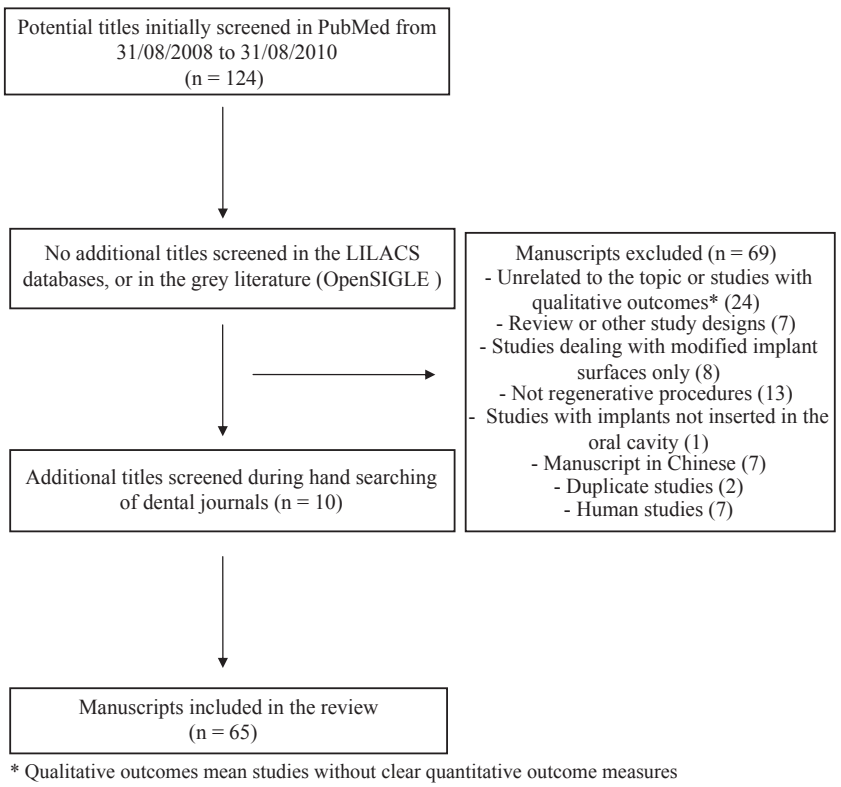
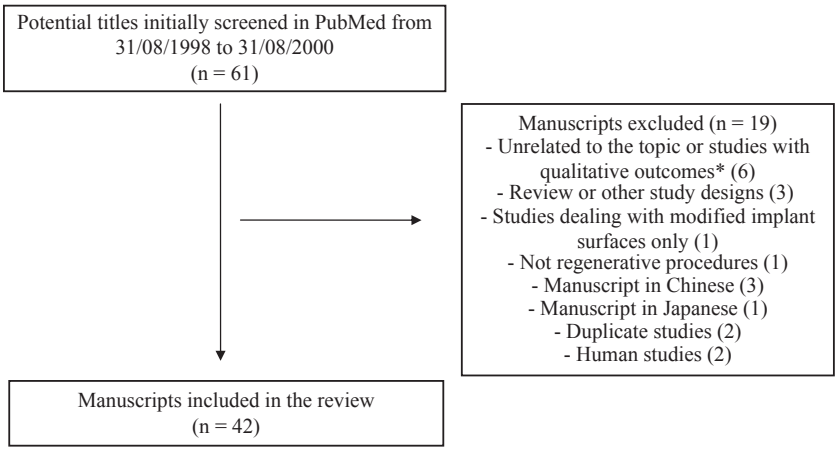


Fig. 1. Flowchart showing the procedure for selection of studies from those published from 2008 to 2010.



* Qualitative outcomes mean studies without clear quantitative outcome measures

Fig. 2. Flowchart showing the procedure for selection of studies from those published from 1998 to 2000.

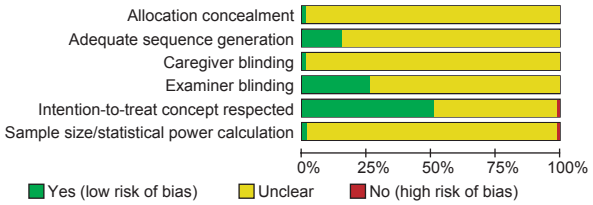


Fig. 3. Review authors' judgement, on the basis of each criterion, of the risk of bias arising, presented as a percentage of the studies published from 2008 to 2010.

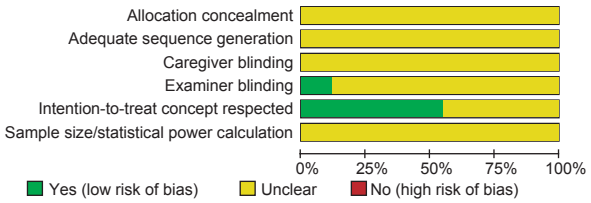


Fig. 4. Review authors' judgement, on the basis of each criterion, of the risk of bias arising, presented as a percentage of the studies published from 1998 to 2000.

Discussion

The results of this study revealed that there is still room for methodological improvement of experiments on animals in periodontology and implantology. Most domains were judged to be at unclear risk of bias and therefore it is not possible to determine the degree of (un)biasedness of the described treatment effects. Note that risk of bias and quality of reporting should be considered distinct from each other. Although the former refers to the internal validity of the trial, the latter refers to how researchers report their findings (Jüni et al. 2001). Ideally, what is reported in the scientific paper should accurately represent what was, in fact, performed in the study. Although direct contact with authors of the study might be an attempt for clarifying dubious or lack of information, this does not guarantee the accuracy of information provided (Haahr and Hróbjartsson 2006). We therefore adopted a conservative approach for assessing the domains; that is, we considered "unclear entries" as unclear risk of bias, although many of these domains would probably be scored at high risk of bias.

To improve the quality of reporting of animal experiments, some guidelines were recently proposed (Schulz et al. 2010). The Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines are based on the CONSORT statement and comprise 20 items to be considered when reporting an RCT of experiments on animals. The guidelines were developed in consultation with scientists, statisticians, journal editors and research funders to enable comprehensive and transparent reporting of animal studies in any area of bioscience research (Kilkenny et al. 2010). As in the CONSORT checklist, ARRIVE gives recommendations for reporting the experiment performed and with respect to every single section of the respective manuscript (title, abstract, introduction, etc.). Improved standards of reporting may reduce the gap between what is reported and what is, in fact, performed. The ARRIVE checklist is described in Table 1. For purpose of comparison, Table S1 (Appendix) reports the original CONSORT checklist.

Sample size calculation was reported for only one of the trials assessed (Valderrama et al. 2010). However, calculation of the sample size might be required for testing the efficacy of new therapies. Studies with low power may generate false-negative results, i.e., so-called type-II errors (Tsang et al. 2009). Our findings confirm and extend previous evidence that shows a lack of reporting regarding sample size calculation in animal studies (Faggion et al. 2009). The low average number of animals in most trials might be partially explained by the difficulty and, probably, high cost of testing, treating and monitoring animals during the study.

Fifty-seven trials (53% of the samples in the studies) were reported as RCTs. For most of the trials, however, the methods used for sequence generation and allocation concealment were not reported, so these domains were judged at unclear risk of bias. Proper randomization is imperative if selection bias is to be prevented (Schulz et al. 1995). In most studies, a split-mouth design was used, and so the authors should have explicitly reported how units (implants or teeth) were allocated within a single animal and whether the sequence was concealed until intervention was assigned

Table 1. Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines for reporting animal experiments in periodontology and implantology (Kilkenny et al. 2010)

	Item	Recommendation
Title	1	Provide as accurate and concise a description of the content of the article as possible
Abstract	2	Provide an accurate summary of the background, research objectives (including details of the species or strain of animal used), key methods, principal findings and conclusions of the study
Introduction		
Background	3	(a) Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale (b) Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology
Objectives	4	Clearly describe the primary and any secondary objectives of the study or specific hypotheses being tested
Methods		
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986) and national or institutional guidelines for the care and use of animals that cover the research
Study design	6	For each experiment, give brief details of the study design, including: (a) The number of experimental and control groups (b) Any steps taken to minimize the effects of subjective bias when allocating animals to treatment (e.g., randomisation procedure) and when assessing results (e.g., if done, describe who was blinded and when) (c) The experimental unit (e.g. a single animal, group or cage of animals) A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: (a) How (e.g., drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s) (b) When (e.g., time of day) (c) Where (e.g., home cage, laboratory, water maze) (d) Why (e.g., rationale for choice of specific anaesthetic, route of administration, drug dose used)
Experimental animals	8	(a) Provide details of the animals used, including species, strain, sex, developmental stage (e.g., mean or median age plus age range) and weight (e.g., mean or median weight plus weight range) (b) Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug- or testnaive, previous procedures, etc.
Housing and husbandry	9	Provide details of: (a) Housing (e.g., type of facility, e.g., specific pathogen free (SPF); type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish) (b) Husbandry conditions (e.g., breeding programme, light/dark cycle, temperature, quality of water etc. for fish, type of food, access to food and water, environmental enrichment) (c) Welfare-related assessments and interventions that were carried out before, during or after the experiment
Sample size	10	(a) Specify the total number of animals used in each experiment and the number of animals in each experimental group (b) Explain how the number of animals was decided. Provide details of any sample size calculation used (c) Indicate the number of independent replications of each experiment, if relevant
Allocating animals to experimental groups	11	(a) Give full details of how animals were allocated to experimental groups, including randomization or matching if done (b) Describe the order in which the animals in the different experimental groups were treated and assessed
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g., cell death, molecular markers, behavioural changes)
Statistical methods	13	(a) Provide details of the statistical methods used for each analysis (b) Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron) (c) Describe any methods used to assess whether the data met the assumptions of the statistical approach
Results		
Baseline data	14	For each experimental group, report relevant characteristics and health status of animals (e.g., weight, microbiological status, and drug- or test-naıve) before treatment or testing (this information can often be tabulated)
Numbers analysed	15	(a) Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%) (b) If any animals or data were not included in the analysis, explain why
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g., standard error or confidence interval)
Adverse events	17	(a) Give details of all important adverse events in each experimental group (b) Describe any modifications to the experimental protocols made to reduce adverse events

Table 1. (continued)

	Item	Recommendation
Discussion		
Interpretation/scientific implications	18	(a) Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature (b) Comment on the study limitations including any potential sources of bias, any limitations of the animal model and the imprecision associated with the results (c) Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research
Generalisability/translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study

(Lesaffre et al. 2007). Some of the studies (n = 50) were controlled trials only, i.e., they were studies with different therapy arms, but without any randomization procedure. In these studies, there is a high likelihood of selection bias occurring. Non-randomized trials tend to generate larger estimates of the effect of treatment than well-designed randomized trials (Kunz et al. 2007). RCTs should therefore be considered the gold standard design for animal experiments.

Caregiver and examiner blinding were not consistently reported. In many cases, however, it is impossible to blind the researcher responsible for delivery of the treatment, because of the impossibility of masking different therapy approaches. In this study, we made no attempt to investigate in detail the real feasibility of blinding caregivers in the studies selected. Nevertheless, some studies (for example Morris et al. 2008) suggest that the material used (in the gel form) might be masked by use of a double-blind design. Although blinding was slightly better reported for the examiner than for the caregiver, most domains were judged at unclear risk of bias. In contrast with blinding the treatment delivered, outcome examination can frequently be masked by use of a researcher not directly involved in the treatment procedures. Examiner blinding is important when measurement of outcome involves some subjectivity (Needleman et al. 2008), for example, quantity of bone formation in histological assessment of peri-implant and periodontal defects.

The intention-to-treat (ITT) principle was not clearly described in most of the experiments. ITT refers to assessment of results for all animals included in the group to which they were allocated, irrespective of whether the intervention was complete (van der Worp et al. 2010). We assume that no animals were withdrawn when researchers reported that healing of surgical procedures was uneventful. In many studies, however, there was no clear description of whether the number of initially included animals was accounted for at the end of the study or not. When the ITT principle is not respected, attrition bias may result in biased estimates of treatment effects (Nüesch et al. 2009).

A possible drawback of our sample may be restrictions resulting from the particular years in which the studies were published. Our selection of publication years may have reduced the representativeness of the sample, but it was necessary to make the assessment of the studies feasible. Nevertheless, as the search strategy chosen was sensitive, our sample may still give a considerably good image of the overall situation.

Moreover, it was decided to assess two temporally different samples to assess whether there was a change within the risk of bias (Scales et al. 2007). Our results suggest that the risk of bias with respect to experiments on animals in periodontology and implantology has improved since the last decade for four of the seven items assessed (Figs 3 and 4). The item "ITT" was derived from the items "all animal accounted for at end of study" and "analysis accounts for animal losses" reported in Tables S2 and S4 (see Appendix, Supporting information), and so only six topics are included in Figs 3 and 4. ITT and "sample size/statistical power calculation" scores seemed comparable for both samples; in the papers published from 2008 to 2010, only one (Valderrama et al. 2010) reported sample size.

Other factors related to trial planning can reduce the methodological quality of a study. For example, the definition of the trial's purpose, i.e., identification of superiority or equivalence is pivotal for the correct interpretation of results. A superiority trial aims at finding whether a new therapeutic approach is more effective than placebo or conventional treatment. An equivalence trial aims at assessing whether a new therapy is comparable to the conventional treatment in terms of efficacy/effectiveness, such that the new therapy could be more efficient (for example, cheaper or easier to use) (Tu et al. 2006). The required sample size of equivalence trials is usually larger than that for superiority trials (Piaggio et al. 2006, Tu et al. 2006). Moreover, not determining the study design a priori will lead to both an incorrect null-hypothesis testing and an inadequate sample size that may yield questionable conclusions.

The assessment of key domains is normally used for assessing risk of bias in human clinical trials. Nevertheless, a similiar rationale may also be applied to animal studies, mainly in those assessing efficacy. Independent of the examined species, shortcomings in the fulfilment of methodological standards such as for example correct sequence generation and allocation concealment, may put studies at high risk of bias.

To summarize, this systematic review has shown that methodological aspects of animal experiments in periodontology and implantology can be improved. Reducing the risk of bias of animal experiments is a pivotal step for providing a sound basis for future human research. We have presented some guidelines that might be useful both to researchers intending to conduct animal experiments and to readers needing to understand the importance of good standards in reporting these trials.

References

Bebarta, V., Luyten, D. & Heard, K. (2003) Emergency medicine animal research: does use of randomization and blinding affect the results? *Academic Emergency Medicine* **10**, 684–687.

Faggion, C. M. Jr, Schmitter, M. & Tu, Y. K. (2009) Assessment of replication of research evidence from animals to humans in studies on peri-implantitis therapy. *Journal of Dentistry* **37**, 737–747.

Faggion, C. M. Jr, Listl, S. & Giannakopoulos, N. N. (2011) The methodological quality of systematic reviews of animal studies in dentistry. *The Veterinary Journal* (in press).

Haahr, M. T. & Hróbjartsson, A. (2006) Who is blinded in randomized clinical trials? A study of 200 trials and a survey of authors. *Clinical Trials* **3**, 360–365.

Higgins, J. P. T. & Altman, D. G. (2009) Assessing risk of bias in included studies. In: Higgins, J. P. T. & Green, S. (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2*. The Cochrane Collaboration. Available at http://www.cochrane.org/training/cochrane-handbook (accessed 15 September 2010).

Jüni, P., Altman, D. G. & Egger, M. (2001) Systematic reviews in health care: assessing the quality of controlled clinical trials. *British Medical Journal* **323**, 42–46.

Kilkenny, C., Browne, W. J., Cuthill, I. C., Emerson, M. & Altman, D. G. (2010) Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biology* **29**, e1000412.

Kunz, R., Vist, G. & Oxman, A. D. (2007) Randomisation to protect against selection bias in healthcare trials. *Cochrane Database of Systematic Reviews* **2**, MR000012.

Lesaffre, E., Garcia Zattera, M. J., Redmond, C., Huber, H., Needleman, I. & ISCB Subcommittee on Dentistry (2007) Reported methodological quality of split-mouth studies. *Journal of Clinical Periodontology* **34**, 756–761.

Morris, M. S., Lee, Y., Lavin, M. T., Giannini, P. J., Schmid, M. J., Marx, D. B. & Reinhardt, R. A. (2008) Injectable simvastatin in periodontal defects and alveolar ridges: pilot studies. *Journal of Periodontology* **79**, 1465–1473.

Needleman, I., Worthington, H., Moher, D., Schulz, K. & Altman, D. G. (2008) Improving the completeness and transparency of reports of randomized trials in oral health: the CONSORT statement. *American Journal of Dentistry* **21**, 7–12.

Nüesch, E., Trelle, S., Reichenbach, S., Rutjes, A. W., Bürgi, E., Scherer, M., Altman, D. G. & Jüni, P. (2009) The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. *British Medical Journal* **339**, b3244.

Pearce, A. I., Richards, R. G., Milz, S., Schneider, E. & Pearce, S. G. (2007) Animal models for implant biomaterial research in bone: a review. *European Cells & Materials Journal* **13**, 1–10.

Pellegrini, G., Seol, Y. J., Gruber, R. & Giannobile, W. V. (2009) Pre-clinical models for oral and periodontal reconstructive therapies. *Journal of Dental Research* **88**, 1065–1076.

Perel, P., Roberts, I., Sena, E., Wheble, P., Briscoe, C., Sandercock, P., Macleod, M., Mignini, L. E., Jayaram, P. & Khan, K. S. (2007) Comparison of treatment effects between animal experiments and clinical trials: systematic review. *British Medical Journal* **334**, 197.

Piaggio, G., Elbourne, D. R., Altman, D. G., Pocock, S. J., Evans, S. J. & CONSORT Group (2006) Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *Journal of Medical Association* **295**, 1152–1160.

Scales, C. D. Jr, Norris, R. D., Keitz, S. A., Peterson, B. L., Preminger, G. M., Vieweg, J. & Dahm, P. (2007) A critical assessment of the quality of reporting of randomized, controlled trials in the urology literature. *The Journal of Urology* **177**, 1090–1094.

Schulz, K. F., Chalmers, I., Hayes, R. J. & Altman, D. G. (1995) Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *The Journal of the American Medical Association* **273**, 408–412.

Schulz, K. F., Altman, D. G., Moher, D. & the CONSORT Group (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* **340**, c332.

Sculean, A., Nikolidakis, D. & Schwarz, F. (2008) Regeneration of periodontal tissues: combinations of barrier membranes and grafting materials – biological foundation and preclinical evidence: a systematic review. *Journal of Clinical Periodontology* **35**, 106–116.

The Nordic Cochrane Centre, The Cochrane Collaboration (2011) Review Manager Software (RevMan Version 5.1). Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.

Tsang, R., Colley, L. & Lynd, L. D. (2009) Inadequate statistical power to detect clinically significant differences in adverse event rates in randomized controlled trials. *Journal of Clinical Epidemiology* **62**, 609–616.

Tu, Y. K., Maddick, I., Kellett, M., Clerehugh, V. & Gilthorpe, M. S. (2006) Evaluating the quality of active-control trials in periodontal research. *Journal of Clinical Periodontology* **33**, 151–156.

Valderrama, P., Jung, R. E., Thoma, D. S., Jones, A. A. & Cochran, D. L. (2010) Evaluation of parathyroid hormone bound to a synthetic matrix for guided bone regeneration around dental implants: a histomorphometric study in dogs. *Journal of Periodontology* **81**, 737–747.

Wang, X., Mabrey, J. D. & Agrawal, C. M. (1998) An interspecies comparison of bone fracture properties. *Bio-Medical Materials and Engineering* **8**, 1–9.

van der Worp, H. B., Howells, D. W., Sena, E. S., Porritt, M. J., Rewell, S., O'Collins, V. & Macleod, M. R. (2010) Can animal models of disease reliably inform human studies? *PLoS Medicine* **7**, e1000245.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. CONSORT checklist (http://www.consort-statement.org).
Appendix S2. Methodological assessment of the first sample (2008–2010) of selected studies on animal experiments on regenerative procedures in periodontology and implantology.
Appendix S3. Characteristics of included studies (2008–2010).
Appendix S4. Methodological assessment of the second sample (1998–2000) of animal experiments on regenerative procedures in periodontology and implantology.
Appendix S5. Characteristics of included studies (1998–2000).
Appendix S6. List of included full-text articles.

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Clinical relevance

Scientific rationale for the study: Every year, many experiments are performed on animals to test the efficacy and potential side-effects of new therapies in dentistry. Assessment of the risk of bias of such studies is therefore of pivotal importance. Such an assessment has, however, not previously been attempted.

Principal findings: The results of this systematic review revealed that it was not possible to accurately determine the risk of bias of the studies included because authors simply did not report the information needed to make the assessment.

Practical implications: Animal research is extremely important in the development of new therapies. Bad reporting generates uncertainty in the risk of bias of experiments with animals and it may compromise the use of the findings of these experiments in human clinical trials.