

SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES



By SYRCLE (www.syrcle.nl)
VERSION 1.0 (JULY 2013)

| Item # | Section/topic | Description | Check for approval |
|--|---|--|-------------------------------------|
| General | | | |
| 1. | Title of the review | Cell-based approaches in periodontal regeneration: A systematic review and meta-analysis of animal studies | <input checked="" type="checkbox"/> |
| 2. | Authors (name, affiliation, contribution) | Xiangzhen Yan ^a , primary researcher Fang Yang ^a , literature examiner Rob de Vries ^b , methodological supervision Jeroen van den Beucken ^a , project director ^a Biomaterials, Radboud University Medical Center ^b SYRCLE, Central Animal Laboratory | <input checked="" type="checkbox"/> |
| 3. | Other contributors (name, affiliation, contribution) | | <input checked="" type="checkbox"/> |
| 4. | Contact person + e-mail address | Xiangzhen Yan (Xiangzhen.yan@radboudumc.nl) | <input checked="" type="checkbox"/> |
| 5. | Date of protocol registration | 13-01-2015 (protocol completed 10-03-2014) | <input checked="" type="checkbox"/> |
| Background | | | |
| 6. | What is already known about this disease/ model/ intervention? Why is it important to do this review? | The regeneration of periodontal tissues remains a challenging clinical problem. Cell-based approaches have been assessed in periodontal regeneration in many animal models with promising results. Nonetheless, no meta-analytical assessment of the relevant literature has been undertaken to quantify the positive effect of cell-based approaches in animal models. Therefore, the purpose of this study is to perform a systematic review of animal studies using cell-based approaches for periodontal regeneration. | <input checked="" type="checkbox"/> |
| Objectives of this SR | | | |
| 7. | Specify the disease / health problem of interest | Periodontal defects | <input checked="" type="checkbox"/> |
| 8. | Specify the population /species studied | Animal models | <input checked="" type="checkbox"/> |
| 9. | Specify the intervention/exposure | Cell-based strategies | <input checked="" type="checkbox"/> |
| 10. | Specify the control population | Scaffold-based strategies | <input checked="" type="checkbox"/> |
| 11. | Specify the outcome measures | New bone, cementum, periodontal ligament formation | <input checked="" type="checkbox"/> |
| 12. | State your research question (based on point 7-11) | What is the efficacy of cell-based approaches, compared to scaffold-based approaches, in animal models for periodontal regeneration? | <input checked="" type="checkbox"/> |
| Methods: | | | |
| Search and study identification | | | |
| 13. | Identify literature databases to search (e.g. Pubmed, Embase, Web of science) | <input checked="" type="checkbox"/> Pubmed <input type="checkbox"/> Web of Science <input type="checkbox"/> SCOPUS <input checked="" type="checkbox"/> EMBASE <input type="checkbox"/> Other, namely [type here] <input type="checkbox"/> Specific journal(s), namely [type here] | <input checked="" type="checkbox"/> |

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| 14. | Define electronic search strategies (e.g. use the step by step search guide [1] and animals search filters [2, 3]) | Please add a supplementary file containing your search strategy: available upon request of the contact author | <input checked="" type="checkbox"/> |
| 15. | Identify other sources for study identification | <input checked="" type="checkbox"/> Reference lists of included studies <input type="checkbox"/> Books <input checked="" type="checkbox"/> Reference lists of relevant reviews <input type="checkbox"/> Conference proceedings, namely [type here] <input type="checkbox"/> Contacting authors/ organisations, namely [type here] <input type="checkbox"/> Other, namely [type here] | <input checked="" type="checkbox"/> |
| 16. | Define search strategy for these other sources | Screening the reference lists for relevant titles and screening the abstracts of these relevant titles | <input checked="" type="checkbox"/> |
| Study selection procedure | | | |
| 17. | Define screening phases (e.g. pre-screening based on title/abstract, full text screening, both) | 1. pre-screening based on titles 2. abstract screening 3. full text screening | <input checked="" type="checkbox"/> |
| 18. | Specify number of observers per screening phase | 1. pre-screening based on titles - 2 observers 2. abstract screening - 2 observers 3. full text screening - 2 observers | <input checked="" type="checkbox"/> |
| Study selection criteria. Define all inclusion and exclusion criteria based on: | | | |
| 19. | Type of study (design) | Inclusion criteria: Data should be presented for cell-based approaches (test) and scaffold-based approaches (control). Exclusion criteria: absence of scaffold-based approaches (control) | <input checked="" type="checkbox"/> |
| 20. | Type of animals/ population (e.g. age, gender, disease model) | Inclusion criteria: animal models with periodontal defects Exclusion criteria: in vitro, human | <input checked="" type="checkbox"/> |
| 21. | Type of intervention (e.g. dosage, timing, frequency) | Inclusion criteria: cell-based approaches Exclusion criteria: other approaches | <input checked="" type="checkbox"/> |
| 22. | Outcome measures | Inclusion criteria: New bone, cementum, periodontal ligament formation Exclusion criteria: other outcome measures | <input checked="" type="checkbox"/> |
| 23. | Language restrictions | Inclusion criteria: all languages Exclusion criteria: none | <input checked="" type="checkbox"/> |
| 24. | Publication date restrictions | Inclusion criteria: all publication dates Exclusion criteria: none | <input checked="" type="checkbox"/> |
| 25. | Other | Inclusion criteria: original paper/primary study Exclusion criteria: not an original paper (review, letter) | <input checked="" type="checkbox"/> |
| 26. | Sort and prioritize your exclusion criteria per selection phase | Selection phase pre-screening based on titles 1. clearly not about periodontal regeneration 2. clearly not about cell-based approaches Selection phase abstract screening 1. original paper 2. in vivo animal studies 3. periodontal regeneration 4. cell-based approaches Selection phase full text screening 1. original paper 2. in vivo animal studies | <input checked="" type="checkbox"/> |

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| | | 3. periodontal regeneration 4. cell-based approaches 5. study design (test and control) 6. other outcome measures 7. no locally applied cells | |
| | Study characteristics to be extracted (for assessment of external validity, reporting quality) | | |
| 27. | Study ID (e.g. authors, year) | authors, year | <input checked="" type="checkbox"/> |
| 28. | Study design characteristics (e.g. experimental groups, number of animals) | experimental groups, number of animals | <input checked="" type="checkbox"/> |
| 29. | Animal model characteristics (e.g. species, gender, disease induction) | species, gender, defect types | <input checked="" type="checkbox"/> |
| 30. | Intervention characteristics (e.g. intervention, timing, duration) | Cell types, amount of cells, cell passage number, scaffold types, duration of follow-up | <input checked="" type="checkbox"/> |
| 31. | Outcome measures | New bone, cementum, periodontal ligament formation | <input checked="" type="checkbox"/> |
| 32. | Other (e.g. drop-outs) | | <input type="checkbox"/> |
| | Risk of bias assessment (internal validity) | | |
| 33. | Define criteria to assess the internal validity of included studies (e.g. selection, performance, detection and attrition bias) | <input type="checkbox"/> By use of SYRCLE Risk of Bias tool <input checked="" type="checkbox"/> By use of SYRCLE Risk of Bias tool, adapted as follows: Items 9 and 10 of the tool will be not scored; two reporting questions will be added: a) Was it stated that the experiment was randomised at any level? b) Was it stated that the experiment was blinded at any level? <input type="checkbox"/> other, namely [type here] | <input checked="" type="checkbox"/> |
| | Data collection | | |
| 34. | For each outcome measure, define the type of data to be extracted (e.g. continuous/ dichotomous, unit of measurement) | Continuous data | <input checked="" type="checkbox"/> |
| 35. | Methods for data extraction/ retrieval (e.g. extraction from graphs, contacting authors) | Outcome data will be extracted if mean, standard deviation (SD) or standard error (SE), and number of defects per group (n) are reported, or can be recalculated. If SE is reported, this SE will be converted to SD for meta-analysis. If data are only presented graphically, data will be re-measured based on the distances of figures using a universal on-screen digitizer software (Universal Desktop Ruler v3.6.3481, AVPSoft.com) when possible. | <input checked="" type="checkbox"/> |
| | Data analysis/ synthesis | | |
| 36. | Specify how you are planning to combine the data (e.g. descriptive summary, meta-analysis) | Meta-analysis | <input checked="" type="checkbox"/> |
| 37. | Specify how the decision as to whether a meta-analysis is appropriate will be made | Meta-analysis will be performed if more than 10 studies can be included | <input checked="" type="checkbox"/> |
| | <i>If a meta-analysis seems feasible:</i> | | |
| 38. | Specify the effect measure to be used (e.g. mean difference, standardized | standardized mean difference | <input checked="" type="checkbox"/> |

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| | mean difference, risk ratio, odds ratio) | | |
| 39. | Specify which study characteristics will be examined as potential source of heterogeneity (sensitivity analysis) | animal species, sex and cell type | <input checked="" type="checkbox"/> |
| 40. | Specify subgroups and comparisons of interest | see item 39; only subgroups that contain more than three experiments will be included in the subgroup analyses. | <input checked="" type="checkbox"/> |
| 41. | Specify method of analysis (<i>e.g.</i> random or fixed effects model) | random effects model | <input checked="" type="checkbox"/> |
| 42. | Specify the method for assessment of risk of publication bias | Publication bias will be assessed by visually evaluating the possible asymmetry in funnel plots. | <input checked="" type="checkbox"/> |
| | Other | | |
| 43. | Describe any expected limitations of your systematic review | poor reporting of animal studies in scientific publications | <input checked="" type="checkbox"/> |

Final approval by:

Xiangzhen Yan (Biomaterials)

Fang Yang (Biomaterials)

Rob de Vries (SYRCLE)

Jeroen van den Beucken (Biomaterials)

Date: 10 March 2014