SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Stem cell therapy in renal ischemia-reperfusion injury – a systematic review of animal studies.	
2.	Authors (names, affiliations, contributions)	Dr. K.E. Wever, SYRCLE, Radboudumc, Nijmegen, The Netherlands T. de Wilt, SYRCLE, Radboudumc, Nijmegen, The Netherlands T. Jorna, SYRCLE, Radboudumc, Nijmegen, The Netherlands A. Tillema, information specialist Medical library Radboudumc M. Ritskes-Hoitinga, SYRCLE, Radboudumc, Nijmegen, The Netherlands	
3.	Other contributors (names, affiliations, contributions)	N/A	
4.	Contact person + e-mail address	K.E. Wever, kim.wever@radboudumc.nl	
5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	02-05-2016	
8.	Registration number (if applicable)	N/A	
9.	Stage of review at time of registration	Screening on title and abstract in progress	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	An impaired renal function has a very big impact on the life of patients. There are ways to help these patients with dialysis but with acute kidney damage the dialysis only offers a temporary solution. When the kidney suffers from ischemia-reperfusion injury the renal functions are greatly impaired. The return of blood and thus oxygen causes inflammation and oxidative damage. This damage and the resulting scarring of the tissue has a big impact on the functionality of the kidney and thus the body's capability to maintain its homeostasis. With stem cell therapy being on the rise in the last decade the possible treatments for acute renal failure are worth investigating. More specifically for the kidney because if the stem cell therapy is proven to heal the damage things like kidney transplantation could be a thing of the past. Stem cell therapy has been proven very effective with heart failure[1] so more attention on renal damage could be promising.	

[1]

		It is important to do this review to try and have the best translation of the animal studies into the pre-clinical trials with human patients. Also the outcome can be used to optimise the animal studies. 1. Tompkins, B., Balkan, W., & Hare, J. M. (2015). Perspectives on the Evolution of Stem Cell Therapy for Heart Failure. *EBioMedicine*, *2*(12), 1838–1839. http://doi.org/10.1016/j.ebiom.2015.11.043	
	Research question		
11.	Specify the disease/health problem of interest	Renal ischemia-reperfusion injury	
12.	Specify the population/species studied	Animals	
13.	Specify the intervention/exposure	Stem cell treatment	
14.	Specify the control population	Animals with renal ischemia-reperfusion injury only	
15.	Specify the outcome measures	Renal damage	
16.	State your research question (based on items 11-15)	Does stem cell treatment reduce renal damage after renal ischemia-reperfusion injury?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed ☐ Web of Science ☐SCOPUS X EMBASE ☐Other, namely: ☐Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	PubMed en EMBASE Search_stem cells AT	
19.	Identify other sources for study identification	X Reference lists of included studies ☐Books X Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	
20.	Define search strategy for these other sources	Reference lists from included studies and relevant reviews will be checked for possibly relevant titles which were not identified by the comprehensive search. Possibly relevant titles will be screened according to the same process as the references identified by the search strategy.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1) Screening for eligibility based on title and abstract 2) Screening for final inclusion based on full-text	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Two observers will independently review each reference. Discrepancies will be resolved by discussion or discussion with a third reviewer.	
	Define all inclusion and exclusion criteria based on:		

23.	Type of study (design)	Inclusion criteria: controlled study with a relevant control group undergoing renal IRI without treatment Exclusion criteria: non-controlled studies, no relevant control group	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: all species and sexes with or without relevant con-morbidity Exclusion criteria: in vitro, in sillico, clinical studies, non-relevant co-morbidity (*i.e.* not relevant to the patient population), genetically modified animals in which the modification does not induce a relevant co-morbidity	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: all types of stem cell treatment, regardless of dose, route of administration, frequency or timing of administration. Exclusion criteria: co-interventions (*e.g.* treatment with EPO in addition to the stem cell treatment)	
26.	Outcome measures	Inclusion criteria: any outcome related to renal injury (functional, histological, biomarkers etc.) and mortality Exclusion criteria: non-renal outcomes (except for mortality)	
27.	Language restrictions	Inclusion criteria: all Exclusion criteria: none	
28.	Publication date restrictions	Inclusion criteria: all Exclusion criteria: none	
29.	Other	Inclusion criteria: full publications presenting original data, of which the full-text can be retrieved. Exclusion criteria: abstracts, publications without original data (*e.g.* most reviews and editorials), full-text not retrievable	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: Title and abstract screening 1. No full publication with original data 2. Not an animal study 3. No renal ischemia-reperfusion model used 4. No stem cell treatment 5. Use of genetically modified stem cells only Selection phase: Full-text evaluation for inclusion Criterion 1-5 with addition of: 6. Non-relevant co-morbidity or co-intervention 7. No relevant outcome measure 8. Article not retrievable	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	1st author, year, title and language	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Experimental groups, number of animals	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Species, sex, co-morbidity y/n, type of comorbidity, duration of renal ischemia, duration of reperfusion (length of follow up/timing of OM)	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Type of stem cell, route of administration, timing of treatment, dose, frequency	

35.	Outcome measures	List all reported outcomes related to kidney injury, record reporting of serum-creatinine, blood urea nitrogen, histology and mortality (Y/N)	
36.	Other (*e.g.* drop-outs)		
	Assessment risk of bias (internal validity) or study quality		
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	Two reviewers will independently assess the risk of bias and reporting of study quality indicators. Discrepancies will be resolved by discussion.	
38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	☐By use of SYRCLE's Risk of Bias tool[4] X By use of SYRCLE's Risk of Bias tool, adapted as follows: In addition we will assess reporting of: any blinding, any randomization, power calculation, temperature regulation and conflict of interest statement. ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☐Other criteria, namely:	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Primary outcome: - Serum creatinine (mg/dl or µmol/L) continuous, or creatinine clearance (µmol/L)/(min) continuous Secondary outcomes: - Blood urea nitrogen (mmol/L) continuous - Histology measured by Jablonski's scale for renal damage or a comparable scale, semi-continuous - Mortality Y/N dichotomous	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1. Direct extraction of data from tables or text 2. Extraction from graphs using digital screen ruler All data will be collected as mean and standard deviation (SD). Standard error will be recalculated to SD. In case of missing data, a conservative estimate will be made whenever possible. If no conservative estimate can be made, the study will be excluded from data-analysis. Authors will not be contacted for additional data to avoid a risk of bias.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	Two reviewers will independently extract the data and check it for inconsistencies. Discrepancies will be resolved by discussion.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	If possible, a meta-analysis will be performed for all outcome measures. If a meta-analysis is not possible the data will be reported by descriptive summary.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	A meta-analysis will be performed if more than 5 studies report on a specific outcome measure. For the subgroup analysis a minimal of 4 studies per subgroup is required.	

	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	For serum creatinine and BUN: when at least ¾ of the studies report baseline data for sham/naive animals, the normalised mean difference (NMD) will be used. If this is not the case the standardized mean difference (SMD) will be used. Histology: raw mean difference (MD) Mortality: risk ratio (RR)	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	Random effects model	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I^2 and R^2	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	- Animal species (stratified per species) - Sex (stratified per sex) - Timing of stem cell administration (stratified pre *versus* post) - Duration of renal ischemia (linear) - Type of stem cell (stratified per cell type) - Dose of stem cells (linear) - Route of administration (stratified per route) - Co-morbidity (stratified Y *versus* N)	
48.	Any sensitivity analyses you propose to perform	SMD analysis if NMD is selected under (44) and *vice versa*. Linear subgroup analysis for timing of stem cells.	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	Correction of p-value for the number of subgroup analyses by Bonferroni-Holmes correction. Correction for multiple comparisons with the same control group by dividing the number of control animals by the number of comparisons with the control group.	
50.	The method for assessment of publication bias	For NMD, MD or RR: produce funnel plots and analyse these plots for outcome measures with at least 20 studies. Funnel plot analysis will not be performed for SMDs because of the risk of funnel plot skewing.	
Final approval by (names, affiliations):		K Wever, T de Wilt	Date: 02-05-2016