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	The effect of analgesics and anaesthetics on the severity of CIPN in animal models	
2.	Authors (names, affiliations, contributions)	Derk Draper Suvarna Gadgil Mehmet Ergun Carlijn Hooijmans Gert Jan Scheffer	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	Derk Draper (derk.draper@radboudumc.nl)	
5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration		
8.	Registration number (if applicable)	-	
9.	Stage of review at time of registration	Data extraction	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Chemotherapy induced peripheral polyneuropathy (CIPN) is a prevalent adverse effect occurring during the treatment of many cancer patients and it seriously affects the quality of life of many patients. Dose adjustments and even termination of the therapy might be necessary in some severe cases. Sometimes, the neurotoxic effects of chemotherapy may be even chronic. To date, no effective therapy has been found for CIPN and only one drug has been recommended for the treatment of CIPN and a alternative treatment is urgently needed. It has been suggested in recent studies that the use of analgesics and anaesthetics might be of potential for treating CIPN and a systematic review of the preclinical models available would be essential for translation the clinic. In this review we will investigate the effect of analgesics and anaesthetics on the severity of CIPN in preclinical models and propose future directions for research about treatment of CIPN.	
	Research question		
11.	Specify the disease/health problem of interest	Chemotherapy induced peripheral polyneuropathy (CIPN)	
12.	Specify the population/species	Non-human animals with induced CIPN receiving the	

	studied	intervention	
13.	Specify the intervention/exposure	Analgesics and anaesthetics (only those that are being used in clinical practice. Drug has to be registered at http://www.farmacotherapeutischkompas.nl/)	
14.	Specify the control population	Non-human animals with induced CIPN receiving no treatment or a vehicle	
15.	Specify the outcome measures	CIPN can be described in various ways: • Mechanical allodynia (e.g. using Von Frey monofilaments) • Mechanical hyperalgesia (e.g. paw pressure test) • Thermal hypo- or hyperalgesia (e.g. tail immersion test, radiant heat assay, tail flick test, cold plate assay) • Sensory-motor coordination (e.g. Rotarod testing) • Nerve conduction • Histological analyses (e.g. neuron counting, studying axonal atrophy and state of myelination, determining Intraepidermal Nerve Fiber Density) • Behavioral changes	
16.	State your research question (based on items 11-15)	What are the effects of analgesics and anaesthetics compared to non-treatment or vehicle on the severity of induced CIPN non-human animal models?	
	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])	When available, please add a supplementary file containing your search strategy: [insert file name]	
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	-	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1) Based on title abstract 2) Based on full text	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a) 2. b) Discrepancies will be resolved by discussion.	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria:	

		• An controlled (independent) animal study for chemotherapy induced peripheral polyneuropathy. It has to be an original study. Exclusion criteria: • Not an original study. • Not a controlled study.	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: • All non-human CIPN animal models (in vivo) will be included. Exclusion criteria: • No animal model used. Ex vivo, in vitro and in silico studies will be excluded. • Not a CIPN model used.	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: • Any dosing regimen of anaesthetic or analgesic will be included in the study. Start of treatment before and after CIPN induction will both be included. Drug has to be registered at http://www.farmacotherapeutischkompas.nl/ Exclusion criteria: • No anaesthetic or analgesic used. • Combination therapies (except for a combination of anaesthetic and analgesic) will be excluded.	
26.	Outcome measures	Inclusion criteria: • All outcomes related to pain as described in item 15. Exclusion criteria: • No outcome related to pain	
27.	Language restrictions	No language restrictions	
28.	Publication date restrictions	No publication date restriction.	
29.	Other	-	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase 1: 1) No original study 2) No animal model 3) No CIPN model 4) No analgesic or anaesthetic used 5) Combination therapy Selection phase 2: 1) No original study 2) No animal model 3) No CIPN model 4) Not a controlled study 5) No analgesic or anaesthetic used 6) Combination therapy 7) No outcome related to pain	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	• First author • Year • Title	

		• Journal • Language	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	• Number of animals • Type of control (non-treated animals or animals treated with a vehicle) ○ Number of animals per group	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	• Species • Strain • Sex • Induction of CIPN (type of chemotherapy, administration route, dose, frequency, duration of treatment) • Weight (or age) • Presence of cancer ○ Type of cancer	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	• Type of analgesic or anaesthetic • Administration route • Dose • Frequency • Duration of treatment • Timing of treatment (relative to CIPN induction)	
35.	Outcome measures	• All outcomes related to pain as described in item 15	
36.	Other (*e.g.* drop-outs)	• Number of drop-outs and reason for dropping out (e.g. death) • Duration of the experiment	
	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	a) 2. b) 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: 1) Addition of reporting of randomisation at any level. 2) Addition of reporting of blinding at any level. ☐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)	Any outcome measure related to pain will be extracted (both dichotomous and continuous).	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	First extraction from text and tables. If not available graphs using a digital screen ruler (http://avpsoft.com/products/udruler/) will be analyzed. Then contacting authors with a maximum of 2 emails.	

41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a) 1. b) Second reviewer will randomly check (5-10%) the extracted data and discuss with first reviewer.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	A meta-analysis with subgroup analysis and sensitivity analysis for all outcome measures will be conducted for all outcome measures. For each outcome measure, two different analyses will be conducted: • In the first analysis, the highest effect (SMD) for each comparison will be included to investigate if analgesics or anaesthetics influence pain sensation. • In the second analysis, acute pain sensation (first 24 hours after administration of analgesics or anaesthetics) over time will be investigated. Outcome data are divided in time periods of one hour and data will be pooled if there are more than one measurements per hour	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	A minimum of two studies is required for performing a meta-analysis for each outcome measure.	
	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)	In case of continuous outcome: • Standardized mean difference (hedges g) (with according 95% confidence interval) In case of dichotomous outcome: • Risk ratio (with according 95% confidence interval)	
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	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	• Species • Sex • Type of CIPN induction • Type of analgesic or anaesthetic used • Administration route Subgroup analyses are only performed when a minimum of 3 studies or 5 independent comparisons are available	
48.	Any sensitivity analyses you propose to perform	Sensitivity analyses will be conducted by excluding conservatively extracted measurements in the meta-analysis. For the second analysis, sensitivity analysis will be conducted by adapting the duration of the time groups to 90 minutes instead of 60 minutes.	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	Holm-Bonferroni correction for multiple testing will be performed. If multiple comparisons are made for the same control group, the amount of animals in the control group will be divided by the amount of comparisons done	
50.	The method for assessment of publication bias	Analyzing funnel plots and performing Duval and Tweedie's trim and fill analysis. This will be done for the 3 outcomes with the largest number of comparisons (a minimum of 10 studies should be present.	

Final approval by (names, affiliations): Carlijn Hooijmans Date: June 2017 Derk Draper