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	Chemotherapy induced (peripheral) polyneuropathy : A systematic review in animal studies	
2.	Authors (names, affiliations, contributions)	1. S. Gadgil, primary researcher † 2. C. Hooijmans, Assistant professor,*† 3. dr. S. Van der Wal, anesthesiologist † 4. S. Van der Heuvel, anesthesiologist† 5. prof. dr. Scheffer, anesthesiologist † * Departments of SYRCLE †Anesthesiology, Radboud University Medical Centre	
3.	Other contributors (names, affiliations, contributions)		
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5.	Funding sources/sponsors	None	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	25 may 2016; Syrcle, Nijmegen	
8.	Registration number (if applicable)	NA	
9.	Stage of review at time of registration	Search, duplicates removed and overall screening for duplicates completed	
	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 (CIPNP) is a painful condition that can even be disabling. 30-40% of the patients receiving chemotherapeutics develop the condition. It is a common factor in limiting or even terminating treatment with chemotherapeutic agents. Therefore treatment or prevention of chemotherapy induced neuropathy is urgently needed. So far, there is no pharmacological therapy available. In order to investigate possible treatments for CIPNP, a complete and structured overview of all various animal models for CIPNP available is needed. Our aims are 1) to conduct this overview by means of a systematic review and 2) to compare the advantages and disadvantages of the various CIPNP models. Note: Summarizing the various animal models is not a regular PICO question, but in order to use this protocol format we will approach the disease induction as the intervention. In order to fulfill our second aim and compare the animal models the Comparator and Outcomes will be used as well.	
	Research question		

11.	Specify the disease/health problem of interest	Aim 1 and 2: PNP	
12.	Specify the population/species studied	Aim 1 and 2:Non human animals	
13.	Specify the intervention/exposure	Aim 1 and 2: Chemotherapy	
14.	Specify the control population	Aim 1: not relevant Aim 2: healthy animal	
15.	Specify the outcome measures	Aim 1: NA Aim 2: Polyneuropathy can be described for example as thermal hypo/hyperalgesia e.g. tail immersion test, radiant heat assay, tail-flick test, or cold plate assay Sensory–Motor Coordination Rotarod testing Electrophysiological testing reduction in nerve conduction velocity (NCV) (**) reduced sensory nerve action potential (SNAP) (**) Mechanical hyperalgesia e.g. paw pressure test von Frey hair test Gait alterations automated gait analysis with the catwalk technique Histopathological - intra epidermal fibre density sciatic nerve: axon diameter and myelin thickness Behavioural changes - changes in grooming - paw licking - aggressive behavior - facial expression -signs of distress - activity (open field test)	
16.	State your research question (based on items 11-15)	Aim 1: What type of chemotherapy induced polyneuropathy animal models are currently used in medical research, Aim 2: In which aspects do animal models for CIPN differ?	
	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	When available, please add a supplementary file containing your search strategy	

	guide[15] and animal search filters[20, 21])		
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) screening based on title 2) screening based on title and abstract 3) full-text screening of the eligible articles	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a. 2 b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Aim 1 and 2: Inclusion criteria: An animal model for chemotherapy induced polyneuropathy is used or described in an original paper. polyneuropathy could be defined by hyper or hypo analgesia (for example cold allodynia, heat hypoalgesia) This could be detected using the tail immersion test Decrease in nerve conduction velocity (NCV) and pathological damages, such as degenerated myelinated axons in the fine nerve fibers of the subcutaneous paw tissue. Exclusion criteria: Not an original study, Not an animal study Not about PNP	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Aim 1 and 2: Inclusion criteria: Any model of chemotherapy given to animals will be suitable for inclusion. Exclusion: not an animal study	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Aim 1 and 2: Inclusion criteria: Animals must receive chemotherapeutics to be able to be included, this means any type of administration. Chemotherapeutics are defined if they are registered on http://www.cancer.gov/about-cancer/treatment/drugs, http://www.farmacotherapeutischkompas.nl/ Exclusion criteria: Not about chemotherapy	
26.	Outcome measures	Aim 1: NA Aim 2: no outcome related to PnP	
27.	Language restrictions	No language restriction	
28.	Publication date restrictions	No date restriction	
29.	Other	Inclusion criteria: original paper/primary study	

		Exclusion criteria: not an original paper (review, letter)	
30.	Sort and prioritize your exclusion criteria per selection phase	Aim 1 and 2: Selection phase: 1. Title screening Articles will be excluded when the article isn't about chemotherapy induced peripheral polyneuropathy (e.g when the title clearly states post-operative pain models or herniation pain model. When in doubt (e.g the title is short and therefore not clear, the article will be included). Selection phase: 2. Screening title/abstract -Exclusion of article and reason will be reported. In case of doubt; paper will be included Note: We will not screen on the presence or absence of specific outcome measures during this phase - In case of doubt article will be included Selection phase 3 Full text screening - we will assess compliance with all eligibility criteria (this means that for aim 2 the outcomes defining PnP will be taken into account) - papers not meeting pre described outcome will be excluded Aim1: Prioritize 1)Not an original paper 2) Not an animal studie 3) Not about chemotherapy 4) Not about PnP Aim 2: 5)No Aspects of PnP described (see outcome measures)	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	1st author year title journal language	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Number of animals Presence of healthy control animal	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Animal Strain Line supplier Sex Animal weight (start & end)	

		co-medication/ co morbidities Method of PnPinduction (mutation / other) Animal age at model induction (if not innate) Time & duration of model induction (for non genetic models)	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Type of chemotherapeutics, Route of administration, dose, frequency, duration of treatment, timing relative to chemotherapy induced polyneuropathy induction,	
35.	Outcome measures	Only for aim 2: All outcome measures related to PnP (qualitative)	
36.	Other (*e.g.* drop-outs)	% survival per group & cause of death Other drop-outs + reason	
	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. Disagreements are solved 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)	Aim 1:Not relevant (summarising animal models, no efficacy study) Aim2: x By use of SYRCLE's Risk of Bias tool[4] ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐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)	For all relevant outcome measures to detect pnp the original data (either continuous or dichotomous) will be extracted.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	first extraction from graphs using a digital screen ruler, then contacting authors	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	2 reviewers, 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)	A descriptive overview of the various models will be given Models will be clustered by induction method (mutation / other), species and strain write and outcome	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	Aim 1: MA is not planned. a descriptive summary of the available animal models for chemotherapy induced polyneuropathy will be the end result	

43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	Aim 1: MA is not planned. a descriptive summary of the available animal models for chemotherapy induced polyneuropathy will be the end result Aim 2: a MA is not planned. However, results of individual studies will be presented in a forestplot.	
	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)	NA	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	NA	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	NA	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	NA	
48.	Any sensitivity analyses you propose to perform	NA	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	NA	
50.	The method for assessment of publication bias	NA	

References

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