SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Systematic review on the technique thoracotomy and post-operative analgesia in animal models with specific focus on mice and rats	
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3.	Other contributors (names, affiliations, contributions)	A. Voncken, CRISP, University Maastricht, The Netherlands W. Basteijns clinical veterinarian University Library support UM: search strategy design	
4.	Contact person + e-mail address	saskia.seeldrayers@maastrichtuniversity.nl	
5.	Funding sources/sponsors	In progress	
6.	Conflicts of interest	None to declare	
7.	Date and location of protocol registration	Maastricht July 2019	
8.	Registration number (if applicable)	-	
9.	Stage of review at time of registration	Preliminary searches started, not completed yet Piloting of the study selection process started, not completed yet Formal screening of search results against eligibility criteria not started Data extraction not started Risk of bias (quality) assessment analysis : not started	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Thoracic surgical procedures are associated with severe post-operative pain and impairment of respiratory functions in humans. In patients acute or chronic post-operative pain are major complication after thoracotomy. Animal models in which thoracic surgery is performed are often used to model human diseases. Pain after	

		thoracotomy has an effect on different physiological parameters. Release of stress induced mediators of inflammation and injury induces complex physiological changes, which play a role in development of post-operative complications including bleeding, hypoxia, myocardial infarction, deep venous thrombosis and pulmonary embolism. Adequate pain relief after a major surgical procedure is important not only for animal welfare but also for reproducible animal model development. With this study we aim to create an overview of the current knowledge on post-operative pain protocols used after thoracic surgery in animal models. By comparing various analgesic techniques in an evidence based manner, we would like to provide more insight in their pain relieving potential and understand better which analgesic protocols might be the most suited for mice or rats.	
	Research question		
11.	Specify the disease/health problem of interest	Post-operative pain after thoracotomy	
12.	Specify the population/species studied	All animal species: focus on laboratory mice and rats	
13.	Specify the intervention/exposure	Analgesic drugs applied for pain relief after thoracotomy: multimodal analgesia or single analgesic: opioids (multimodal) , non opioid analgesics (such as NSAIDS, metamizole ,paracetamol), other drugs for acute pain management (such as ketamine, lidocaine)	
14.	Specify the control population	Preferred control group: animals with thoracotomy not receiving analgesia All other controlled or non controlled studies will be included in the review for descriptive analysis.	
15.	Specify the outcome measures	Body weight and other physiological parameters indicative for pain or post-operative recovery	
16.	State your research question (based on items 11-15)	What's the effect of different analgesic protocols on post-operative pain relief after thoracotomy in animals with a specific focus on mice and rats Subquestion: Is there a role for metamizole, ketamine or local anesthetics?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	xMEDLINE via PubMed xWeb of Science □SCOPUS xEMBASE □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	xReference lists of included studies □Books xReference lists of relevant reviews □Conference proceedings, namely: □Contacting authors/ organisations, namely: □Other, namely:	
20.	Define search strategy for these other sources	Reference lists will be screened for interesting titles. Relevance of papers will be screened in the same way as performed in the papers retrieved by initial search.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	After removal of duplications First Phase: Pre-screening on title to remove obvious irrelevant references on the review topic Second phase: Screening on title and abstract Third phase: screening full text on in and exclusion criteria.	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	2 reviewers (SS, AV, AT) for each screening phase. In case of discrepancies, a third reviewer will be consulted	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: original published articles Exclusion criteria: In vitro studies, non survival studies, short term follow up time (less than 24 hours)	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: all animal studies Exclusion criteria: human studies	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: analgesia Exclusion criteria: no information available/ retrievable on procedure (thoracotomy), analgesics and anesthetics used. unsuitable co-intervention such as initial surgery before thoracotomy without sufficient recovery (<14d) period.	
26.	Outcome measures	Inclusion criteria: any outcome parameter related to post-operative recovery or pain assessment, e.g. clinical assessment, pain scoring systems, pain related behaviour, physiological parameters, stress induced mediators of inflammation and injury Exclusion criteria: no report of outcome parameter related to post-operative recovery or pain assessment	
27.	Language restrictions	No restrictions	

28.	Publication date restrictions	No restrictions	
29.	Other	Inclusion criteria:- Exclusion criteria: not a primary study with original data (review)	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase I: Pre-screening on title to remove obvious irrelevant references on the review topic Selection phase II: title, abstract 1. Not an in vivo animal study: human, in vitro, ex vivo 2. Not an original full publication (abstract, review) 3. No thoracotomy performed 4. Non survival experiments, short term follow up time (less than 24 hours) Selection phase III: full text 1. Not an in vivo animal study: human, in vitro, ex vivo 2. Not an original full publication (abstract, review) 3. No thoracotomy performed 4. Non survival experiments, short term follow up time (less than 24 hours) 5. no information available/ retrievable on procedure (thoracotomy), analgesics and anesthetics used. 6. no relevant outcome measure reported: outcome not relevant for behavioural or physiological assessment of post-operative recovery or pain. 7. unsuitable co-intervention applied 8. full article not retrievable	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Author, title, year of publication	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Number of animal groups (intervention and control) number of animals per group, number of animals per cage, housing and husbandry conditions	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Species, strain, age, gender, genetical condition, health status, disease induction/model	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Surgery related: Anesthesia method used, intubation performed, artificial or spontaneous ventilation (including settings), anesthetic monitoring, Surgical approach, duration surgery, suture techniques. Post-operative supportive care, post-operative analgesia (dose, application route, frequency, duration)	
35.	Outcome measures	Time and frequency of outcome assessments, type of outcome measures, only outcome measures which are quantifiable will be included	

36.	Other (*e.g.* drop-outs)	Drop out, complications during and after surgery	
	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	At least 2 reviewers will assess risk of bias and study quality. In case of discrepancies a third reviewer will be consulted	
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] xBy use of SYRCLE's Risk of Bias tool, adapted as follows: additional scoring on reporting of randomisation, reporting of any blinding and reporting of power calculation. □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)	We expect the review to be descriptive. Any outcome related to post-operative recovery or pain will be extracted.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1. From text 2. From graphs 3. If necessary, the authors of the article may be contacted	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	At least 2 persons will extract data. In case of disagreement a third person will be consulted for review	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Data will be compared using a descriptive summary of all included studies and their outcome measures used. A meta-analysis will be performed if there are sufficient studies (5 or >) with the same or similar outcome measures.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	If 5 or more studies are included using the same or similar outcome measures, a meta-analysis will be performed	
	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)	To be determined depending on outcome parameter In case of continuous outcome: mean value for each group, standard deviation for each group and number of animals per group will be documented Standardized mean difference (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)	Heterogeneity will be assessed using I^2 values	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Surgical approach, type of analgesic used, Species/ Strain differences, sex, type of treatment (onset/duration/ administration route, frequency), time observation	
48.	Any sensitivity analyses you propose to perform	To be determined	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	To be determined	
50.	The method for assessment of publication bias	Funnel plot	
Final approval by (names, affiliations):		All	Date: 16-09-'19