INPLASY PROTOCOL

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None declared.

Animal models for seroma- and subcutaneous dead space prevention after surgery; a systematic review and meta-analysis protocol

Poos, SEM[1]; Hermans, BP[2]; van Goor, H[3]; ten Broek, RPG[4].

Review question / Objective: **1. What animal models have previously been used to assess the effectiveness of an intervention in dead space obliteration and seroma prevention, and what are the methodological characteristics of these models? 2. What is the risk of bias of previous studies that used animal models to assess effectiveness of an intervention in dead space obliteration and seroma prevention, based on the SYRCLE Risk of Bias tool?**
Condition being studied: **Seroma is a well-known complication after surgical intervention, with up to 85% of patients experiencing seroma formation after mastectomy, up to 53% after abdominoplasty, and up to 50% after ventral hernia repair. Seroma can occur when a subcutaneous dead space is created after removal of a substantial amount of soft tissue, in which seroma fluid can accumulate. This may cause for significant patient's discomfort, need for repeat hospital visits, prolonged drainage need, frequent aspirations, and possible readmissions and reoperations. It has been suggested that the increased inflammatory cytokine production in seroma maintains the fluid and cause discomfort and pain. Complaints are aggravated when the seroma fluid becomes infected which may result in wound dehiscence and delayed wound healing.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 January 2023 and was last updated on 24 January 2023 (registration number INPLASY202310075).

INTRODUCTION

Review question / Objective: **1. What animal models have previously been used to assess the effectiveness of an intervention in dead space obliteration and seroma prevention, and what are the methodological characteristics of these models?**

2. What is the risk of bias of previous studies that used animal models to assess effectiveness of an intervention in dead space obliteration and seroma prevention, based on the SYRCLE Risk of Bias tool?

Rationale: Seroma is one of the most common complications for patients undergoing various surgical interventions (e.g., mastectomy, lumpectomy, abdominoplasty, lattisimus dorsi harvest, hernia repair, etc.). Surgeons use a broad selection of products and techniques to prevent the formation of seroma, with mixed results. In literature, a significant amount of interventions are proposed to obliterate dead space and/or to prevent seroma formations, and many make use of animal models to provide a proof of principle. However, the translatable value of data received from these animal studies to the clinical situation is notoriously debatable. This is mostly caused by the heterogeneity in animal models described in literature, as well as the inability of most studies to rule out the existence of bias in the experimental method. A systematic review and meta-analysis on previously used animal models for a specific pathological condition is key to intercepting both of these problems, as a systematic review can identify the varieties in methodology and outcome measures between studies, as well as displaying the risk of bias of previous related literature. In this systematic review, we aim to provide a complete overview of the methodological characteristics of previous animal models used to test the efficacy of interventions for preventing seroma formation. Furthermore, we aim to define the different risks of bias that previous animal models display by using SYRCLE's Risk of Bias tool. Lastly, we aim to provide reasonable improvements and recommendations for future animal studies related to seroma prevention, which can increase the methodological homogeneity and significantly decrease the bias risk, which may result in a higher translatable value towards the clinic.

Condition being studied: Seroma is a well-known complication after surgical intervention, with up to 85% of patients experiencing seroma formation after mastectomy, up to 53% after abdominoplasty, and up to 50% after ventral hernia repair. Seroma can occur when a subcutaneous dead space is created after removal of a substantial amount of soft tissue, in which seroma fluid can accumulate. This may cause for significant patient's discomfort, need for repeat hospital visits, prolonged drainage need, frequent aspirations, and possible readmissions and reoperations. It has been suggested that the increased inflammatory cytokine production in seroma maintains the fluid and cause discomfort and pain. Complaints are aggravated when the seroma fluid becomes infected which may result in wound dehiscence and delayed wound healing.

METHODS

Search strategy: A three-component search strategy is developed and used in Pubmed and Embase, which are: "Animal model", "Adhesive and other possible interventions", and "seroma and subcutaneous dead space". For the first component, we make use of the updated animal model search filter created by SYRCLE.

Participant or population: All animal models mentioned in literature (mammals).

Intervention: All possible interventions used to obliterate dead space and/or prevent seroma formation.

Comparator: All control populations used in the described studies.

Study designs to be included: Only in-vivo mammal study designs.

Eligibility criteria: Inclusion criteria: 1) In-vivo study design in mammals; 2) Surgical procedure promoting seroma or creating a subcutaneous pocket or -dead space; 3) Assessing seroma- or dead space formation both quantitatively as qualitatively as outcome measure. Exclusion criteria: 1) Veterinary studies 2)

Conference abstract; 3) Surgical method in which the peritoneum is (partially) compromised; 4) Percutaneous wound healing model; 5) Subcutaneous implant model.

Information sources: The databases Pubmed and EMBASE (both 1980-present) were used for the search of relevant studies. Search strategy was subdivided in three distinct parts: 1) The SYRCLE animal filter was used to search for all animal models available. 2) To search for all interventions used to prevent seroma formation and to obliterate subcutaneous dead space, terms related to tissue adhesives and other interventions that prevent seroma formation (e.g., negative pressure therapy, sutures or a suturing technique, platelet rich plasma, etc.) were used. 3) Terms related to seroma- and subcutaneous dead space formation were used to search for all studies related to seroma as a pathological phenomenon. Effort was made to identify the full-text of all studies relevant to the objective, e.g. by translating non-English studies, checking the references of retrieved studies to determine potential inclusions, appealing to libraries worldwide, etc. Conference abstracts were excluded as too little data could be extracted. Veterinary clinical studies were excluded.PubMed, MEDLINE, EMBASE. We will make an extensive effort to retrieve all suitable full-texts with the help of the Radboud UMC medical library.

Main outcome(s): For Research Question 1: Animal model usage (species, weight, age, sex, animal number), method structure (ARRIVE guidelines), surgical procedure for dead space/seroma formation (anatomical region, defect dimensions, hemostatic measures), intervention type, macroscopic assessment of dead space and/or seroma, seroma volume (measured pre- or post-mortem). The Risk of Bias Tool will be used to answer Research Question 2 (see below).

Data management: Citation will be collected and sorted in EndNote 20, data regarding the main outcomes will be pooled from all included studies in a database in IBM SPSS Statistics.

Quality assessment / Risk of bias analysis: Risk of bias analysis will be done with the help of the Risk of Bias Tool, designed by SYRCLE. Two researchers will assess the risk of bias (ROB) of all studies independently using this tool, after which consensus will be reached over the ROB grading for the complete dataset by means of discussion. Eight risks will be graded: 1) Random allocation sequence design; 2) Confounder adjustments; 3) Allocation concealment; 4) Random housing; 5) Blinded caregivers; 6) Random outcome assessment; 7) Blinded outcome assessor; and 8) Incomplete outcome data. Next to this, surgical quality of the intervention will be assessed by displaying the mentioning of ethical approval, housing, description of anesthesia measures, post-operative analgesia, antibiotics and sterility during surgery. Also, internal validity will be assessed by eight additional questions: randomization, blinding, presence of positive- and negative control, power calculation, company funding, data access, and protocol registration. All these questions are answered with either 'yes', 'no', or 'unclear'. Publication bias will be assessed by authors own conclusions, and is qualified by either 'positive', 'negative', 'neutral', or 'non-conclusive'. Additionally, a reporting quality scoring system based on the ARRIVE guidelines and similar to a previous systematic review will be designed to quantify the overall report quality. The score is a sum of all mentions of the following 19 items in an article: Presence of positive or negative control, sample size, power calculation, animals per experimental group, randomization, blinding, statistical methods used, species, sex, weight, age, surgical procedure, suture technique and/or material, defect location and/or dimensions, ethical approval, housing, sterility during surgery, protocol registration and data access.

Strategy of data synthesis: Data will be collected from the included articles into a database containing multiple parameters based on previously mentioned outcome

measures. Results will be statistically assessed on their differences by using various methods, like the student T-test, ANOVA, and Tukey's HSD post hoc test. $P<0.05$ will be considered statistically significant. A meta-analysis will be performed within subgroups that use similar animal models. In this meta-analysis we will assess seroma incidence as well as the mean seroma volume in both the control- and intervention groups. We will use the inverse variance method for pooling the incidences and to calculate the odds ratio and corresponding 95% confidence intervals. Fixed effect- (Mantel-Haenszel) and random effect models will be used for comparison of seroma incidence between intervention and control groups. The standardized mean difference is used as effect measure for comparison of seroma volumes between intervention and control groups. Software used for data collection, data comparison, plot generation and statistical analyses were IBM SPSS Statistics, R for Windows and RStudio.

Subgroup analysis: Studies describing a surgical model with seroma volume as outcome measure are used for a separate analysis. Furthermore, distinctions in intervention (tissue adhesive, mesh, suturing technique, negative pressure wound therapy) and surgical location (face, neck, chest, back, abdomen, lower body) are made.

Sensitivity analysis: No sensitivity analysis was performed in this study.

Language restriction: None. All non-English articles are translated to English using DeepL translator (www.deepl.com), and consequently analyzed for inclusion.

Country(ies) involved: The Netherlands.

Keywords: Seroma; Subcutaneous dead space; Animal model; In-vivo; Systematic review; Meta-analysis.

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