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Research review

Current insights into extracorporeal perfusion of free tissue flaps and extremities: a systematic review and data synthesis

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ABSTRACT

Background: Extracorporeal perfusion is a promising new technique for prolonged preservation of free flaps and extremities; however, uncertainties on perfusion settings and efficacy still exist. No overview of literature is currently available. This review systematically appraised available evidence comparing extracorporeal perfusion to static storage.

Materials and methods: An electronic systematic search was performed on June 12, 2016, in MEDLINE and EMBASE. Articles were included when evaluating the effect of extracorporeal perfusion of free flaps or extremities compared to that of a control group. Two independent researchers conducted the selection process, critical appraisal, and data extraction.

Results: Of 3485 articles screened, 18 articles were included for further analyzation. One article studied discarded human tissue; others were studies conducted on rats, pigs, or dogs. Perfusion periods varied from 1 h to 10 d; eight articles also described replantation. Risk of bias was generally scored high; none of the articles was excluded based on these scores. Tissue vitality showed overall better results in the perfused groups, more pronounced when perfusing over 6 h. The development of edema was a broadly described side effect of perfusion.

Conclusions: Although tissue vitality outcomes seem to favor extracorporeal perfusion, this is difficult to objectify because of large heterogeneity and poor quality of the available evidence. Future research should focus on validating outcome measures, edema prevention, perfusion settings, and maximum perfusion time for safe replantation and be preferably performed on large animals to increase translation to clinical settings.

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Introduction

Numerous advancements have been made over the last few decades in the field of transplant medicine. A new technique for solid-organ preservation was introduced by means of machine perfusion with superior results compared to cold storage (CS).[1,2] This trend was followed in the domain of free flap and extremity transplantation since the 1980s, when experiments on extracorporeal perfusion techniques commenced in these tissues.[3,4]

Muscle is the tissue most sensitive to ischemia and reperfusion injury, with a maximum ischemia tolerance of 4 to 6 h, followed by nerves with a tolerance of approximately 8 h.[5] The current standard of preservation of free flaps or extremities is CS (±4°C), preferably after a heparin-solution flush to washout blood and prevent intravasal clotting. It is hypothesized that preservation of free flaps and extremities can be enhanced by extracorporeal perfusion, either by using cellular preservation fluids or blood products. Proposed mechanisms are protection of the endothelial cell lining of blood vessels, dilution and prolonged washout of toxic metabolites, and buffering capacities of the perfusion solutions for toxic metabolites.[6,7] Optionally, the perfusion solution is cooled, thereby slowing cell metabolism and reducing oxygen needs of the tissue. Also, oxygen can be added to the perfusion solution to maintain aerobic cell metabolism.[8,9]

The ultimate goal of extracorporeal perfusion is to lengthen the ischemic period of free flaps or extremities with hours or even days. This enables vascularized composite allotransplantation to come into closer reach, for instance, of extremities or the face. In addition, unexpected intraoperative complications can be treated, and time becomes available for stabilization or transportation of patients with traumatic amputations (e.g., war victims).[10-12] Some authors even foresee the use of extracorporeal perfusion for transplantation of tissue to areas depleted of acceptor vessels (e.g., radiated tissue), maintaining flap viability for days until neovascularization of the transplanted tissue has occurred.[13]

Despite these exciting applications of extracorporeal perfusion and on-going preclinical trials, many uncertainties on its efficacy and use still exist, and an overview of currently available literature is missing. The aim of this review therefore is to systematically appraise the available evidence comparing tissue vitality in extracorporeal perfused free flaps and extremities to the nonperfused control groups. Previous preclinical systematic reviews have proven to be useful in hypothesis generation and in optimizing the design of both preclinical and clinical studies. Therefore, the second aim of this article was to provide directions for further research, aiming to improve the quality of research in the field of extracorporeal perfusion.[14]

Materials and methods

The protocol for this review was registered on the website of the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE, Nijmegen) before starting data extraction.[15] An electronic systematic search was performed in MEDLINE (1946 to present) and EMBASE (1947 to present) using a combination of 'free flaps'/'extremities' and 'extracorporeal perfusion' with synonyms (Appendix A). The first author (A.S.K.) designed the search strategy with support from a librarian. No publication date or language restrictions were applied. All articles were collected into a single reference library (Endnote X7.7.1, Thomson Reuters, New York, NY) and duplicates were removed. Two independent reviewers (A.S.K. and H.W.) first screened the articles on title and abstract, followed by a full-text screening, resulting in a selection of relevant articles. Final consensus was reached by deliberation between both the reviewers. Cross-reference search and citation check were performed to identify additional articles.

Original articles evaluating the effect of extracorporeal perfusion of free flaps or extremities of both animals and humans were included in the review. Extracorporeal perfusion was defined as a (semi-)closed circuit containing a fluid for continuous tissue preservation with regulated pressure or flow, with or without oxygen supply. Subjects receiving a single flush with preservation solution rather than continuous perfusion were not included in this review nor were articles without a control group. The primary outcome was tissue vitality, which was further divided into the following three categories: histology, serum markers, and tissue function. The secondary outcome was edema/weight gain. Edema is a known side effect of machine perfusion, which might impede the replantation procedure and influence results after replantation when present at a high degree. Weight gain was extracted from the data as percentage of weight increase based on the tissue's original weight.

The two independent reviewers critically appraised and extracted data from all included articles. A short deliberation between the reviewers followed on five articles until consensus was reached. The SYRCLE's risk of bias tool[16] was used for risk of bias assessment at study level, expanded with the following criteria: statement on compliance with animal welfare regulations, sample size calculation/*post hoc* power analysis performed, and statement on conflicts of interests. Each criterion was scored with Yes (Y), No (N), Unknown (?), or Not Applicable (N/A). Extracted data included study characteristics and design, animal/patient characteristics, intervention characteristics, outcomes for tissue viability, tissue function and edema, dropouts, and presence of a sample size calculation. Data were extracted directly from text or tables or were derived from graphs using a digital screen ruler. In case of incomplete or unclear outcomes in the included articles, corresponding authors were contacted by e-mail twice at a 2-wk interval. For data synthesis, articles were imported and analyzed in Review Manager (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). There was an intention to conduct a meta-analysis; however, this appeared to be impossible based on predefined criteria[15] because of the large heterogeneity in study group characteristics, study design, and follow-up. Instead, two summarizing forest plots were composed to provide a cumulative overview of data for histology and edema.