Transplantation Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

Remote ischemic preconditioning of transplant recipients to reduce graft ischemia and reperfusion injuries: A systematic review☆

Waqas Farooqui [a,*,1], Hans Christian Pommergaard [b,2], Allan Rasmussen [b,3]

[a] Department of Surgery, Nordsjællands Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark
[b] Department of Surgical Gastroenterology and Transplantation, Abdominal Centre, Rigshospitalet, Blegdamsvej 9, 2100 København Ø, Denmark

A B S T R A C T

Background: Solid organ transplantation is an accepted treatment for end-stage solid organ diseases. During the procedure, ischemia and reperfusion injury may affect graft and patient outcomes. Remote ischemic preconditioning (rIC) has been shown to reduce ischemia and reperfusion injury and can be performed safely. Thus, rIC may potentially improve outcomes after solid organ transplantation. Traditionally, the focus of rIC has been on the donor. However, preconditioning the recipient may be a more suitable approach in transplant settings. The current review analyzed previously published studies where rIC was performed on transplant recipients.
Methods: PubMed and EMBASE databases were searched for eligible clinical and animal studies evaluating rIC of recipients. Articles were analyzed and compared qualitatively. Risk of bias was assessed using the Cochrane Collaboration's tool for interventional clinical studies and SYRCLEs risk of bias tool for animal studies.
Results: A total of 12 studies were included. Overall, these studies were heterogeneous due to differences in populations and intervention set-up. Some of the studies suggested improvement of graft function, while other studies did not show any effect. The quality of the 12 included studies was predominantly low.
Conclusion: Due to the heterogeneity and quality of the included studies the result, that rIC may be beneficial in transplantation of some organs, should be interpreted with caution. The result must be confirmed by further clinical studies.

1. Introduction

Solid organ transplantation is an established treatment for end-stage solid organ diseases. However, due to the nature of the procedure, ischemia and reperfusion injuries (IRI) remain a critical clinical issue. IRI is a major cause of delayed graft function and primary graft dysfunction. IRI may also result in acute and chronic graft rejection, as well as increased long-term morbidity and mortality [1,2]. Treatments for and prophylactics against IRI are in the experimental stages. However, ischemic preconditioning (IPC) may be a safe, cheap, and efficient approach.

Immense research on IPC shows it efficiently reduces injuries resulting from ischemia and reperfusion [3]. This technique has proven to be effective, especially within the fields of cardio- and neuroprotection [3,4]. IPC has also shown good results when applied locally on a specific organ and when applied remotely [5–9]. However, the underlying mechanisms of remote ischemic preconditioning (rIC) are not fully understood.

Current concepts suggest a complex combination of circulating (humoral) mediators and neuronal signaling responsible for conditioning of the target organ [10,11]. It is unclear whether humoral mediation and neuronal signaling play equivalent or time-dependent, alternating roles in rIC. Literature suggests humoral mediators play a systemic and local part [12], and inhibition of pre- and postganglionic transmission in the autonomic nervous system abolishes rIC-induced organ protection [12,13]. In addition, blocking transmission through the spinal cord and vagal nerves has been shown to abolish organ protection. Some studies suggest that activation of vagal nerves is needed for the activation of humoral mediators [14].

Nonetheless, there appears to be a consensus regarding the final, common pathway by which IPC, including rIC, exerts its protective effect. This involves a cascade of intracellular protein kinases which results in the opening of adenosine triphosphate-sensitive potassium channels and reduced mitochondrial transition pore permeability. Activation of this cascade also increases expression of anti-inflammatory mediators, thereby causing an immediate and delayed conditioning response [15].

In the field of solid organ transplantation, local IPC of a transplanted organ is only possible through invasive procedures, while rIC represents a reasonable, noninvasive alternative. IPC is applied by intermittently occluding and re-opening blood flow to the target organ. This is done for a set time period and for a set number of cycles. Preconditioning implies that the procedure is done before the ischemic episode. In

☆ Funding sources: This paper was not funded or sponsored in any way
* Corresponding author at: Parkhøjvej 4, 2 TV, 2800 Lyngby, Denmark.
E-mail address: wf@regionsjaelland.dk (W. Farooqui).
[1] Designed study, wrote paper, analyzed data, approved final version
[2] Designed study, revised paper, approved final version
[3] Designed study, analyzed data, revised paper, approved final version

http://dx.doi.org/10.1016/j.trre.2017.06.001
0955-470X/

Please cite this article as: Farooqui W, et al, Remote ischemic preconditioning of transplant recipients to reduce graft ischemia and reperfusion injuries: A systematic review, Transplant Rev (2017), http://dx.doi.org/10.1016/j.trre.2017.06.001

contrast to local IPC, rIC is applied away from the target of ischemia, for example, by using a blood pressure tourniquet on an extremity. rIC has shown good results in attenuating IRI caused during solid organ transplantation [16].

However, most previous studies have been done on the graft donor [17]. During transplantation, the graft is flushed to cleanse the organ of blood before storage and introduction into the recipient [18,19]. Therefore, circulating mediators involved in the reduction of IRI may be flushed too. Preconditioning of the recipient, on the other hand, would allow mediators to stay in the blood and reach the graft when reperfused. Interestingly, since neuronal signaling also appears to play a part in conditioning, it is possible IPC should be applied to both the donor and recipient. To clarify whether rIC of the recipient alone has an effect on IRI in transplant settings, we reviewed all available clinical and animal studies on the subject.

2. Methods

The current review was reported in accordance with the PRISMA statement [20]. Analytical methods and inclusion criteria were specified in advance and registered at PROSPERO (registration no., CRD42016040083).

2.1. PICOS

(P)opulation: Recipients (humans and animals) undergoing solid organ transplantation
(I)ntervention: rIC
(C)omparison: no rIC
(O)utcome: IRI in the graft
(S)tudies: Randomized and prospective controlled animal and clinical trials

2.2. Eligibility criteria

Included studies were required to be prospective, randomized clinical or animal trials written in English that evaluated solid organ transplant recipients (human or animals) who received rIC (versus non-rIC recipients) and experienced graft IRI. Retrospective studies were excluded.

PubMed [National Library of Medicine (1966 – present)] and EMBASE (1974 – present) databases were both searched for articles meeting the above criteria on April 5, 2016. The development of the search strategy was done as a collaboration between all three authors. The search string used in PubMed was as follows:

((((((((((("Transplant Recipients"[Mesh]) OR recipient) OR recipients))))) OR (transplantation) OR grafting)))) AND (((((((ischemic preconditioning"[Mesh]) OR ischemic conditioning) OR preoperative ischemia) OR pretransplant ischemia)))))

A similar search string was used on EMBASE:

((organ transplantation or transplantation or transplant or recipient or transplant recipient or graft recipient) and (ischaemia or ischemia or ischemic) and (conditioning or preconditioning or pre-conditioning or ischemic conditioning or ischemic preconditioning or ischemic preconditioning)).af.

Assessment of the abstracts and their eligibility was performed independently and in an unblinded, standardized manner. Available full-text articles corresponding to eligible abstracts were obtained and evaluated in detail. Disagreements between the reviewers were resolved by consensus. The reference lists of all included articles were scanned for additional studies of relevance. No contact with authors was needed. ClinicalTrials.gov was searched on April 20, 2016, for ongoing trials using the term "*ischemic conditioning transplantation*".

2.3. Data collection process

A data extraction form was generated and utilized for each eligible study. A data extraction table was also generated to include important items needed. Extracted data is listed in the data extraction tables (Appendices 1 and 2).

2.4. Risk of bias in individual studies

Depending on the population used in each study, either the Cochrane Collaboration's tool for interventional clinical studies [21] or Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool for animal studies [22] was used. The Cochrane Collaboration's tool for interventional clinical studies assesses the risk of bias in randomized, controlled trials and addresses the following types of bias: selection, performance, attrition, detection, and reporting. Bias subtypes are assessed as "low risk," "high risk," or "unclear." The SYRCLE tool was developed to evaluate the risk of bias for animal studies resembling the Cochrane Collaboration's tool for interventional clinical studies. The assessment is out of 10 points, and the presence of a bias is evaluated with a "yes," "no," or "unclear."

2.5. Data synthesis

Since the populations, interventions, methods, and reported outcome measures varied markedly in the eligible studies, a meta-analysis was not considered appropriate. Thus, a qualitative analysis was conducted.

3. Results

An initial search of PubMed and EMBASE yielded a total of 3260 references; 435 were included for full-text screening. Of the 435 references, 418 were discarded due to inappropriate study design, outcomes, or interventions. Thus, full-text screening resulted in 17 relevant studies. After removing any duplicates, the reference lists of the 17 studies were screened. As a result, 12 studies were included in the current systematic review. The study selection process is shown in Fig. 1.

Of the seven clinical studies, all were stated to be randomized. One was only published as an abstract [23], one was published as a letter to the editor [24], and one was a pilot study reported in a review focusing on the potential effects of rIC on kidney injuries after kidney transplantation [25]. Not all data was reported for these three studies. Another study was still ongoing the day the online databases were searched but was later completed and published on October 3, 2016 [26]. Of the five animal studies, all trials were stated to be randomized.

3.1. Risk of bias within studies

The seven clinical studies were evaluated for risk of bias with the help of Cochrane's tool; all seven were reported as randomized. Reporting of allocation concealment and sequence generation was limited in four of the studies. Two [26,27] mentioned the randomization process and process of concealment. Five out of the seven studies reported blinding the research personnel. Information on reporting bias was unclearly stated in five of the seven studies. The two most recent studies [26,27] published their protocols in advance, allowing comparison. An overview of the assessment of risk of bias in clinical studies is present in Table 1.

Due to the lack of reporting, the results from five of the seven clinical studies have a risk of selection bias. The type of primary outcome in each study is such that detection bias is irrelevant. Information on reporting bias was unclearly stated in most of the studies. The risk of concealing important results is therefore possible.

Please cite this article as: Farooqui W, et al, Remote ischemic preconditioning of transplant recipients to reduce graft ischemia and reperfusion injuries: A systematic review, Transplant Rev (2017), http://dx.doi.org/10.1016/j.trre.2017.06.001