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Clinical Practice

Propofol-based anaesthesia *versus* sevoflurane-based anaesthesia for living donor kidney transplantation: results of the VAPOR-1 randomized controlled trial

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Abstract

Background. Kidney transplantation is associated with harmful processes affecting the viability of the graft. One of these processes is associated with the phenomenon of ischaemia–reperfusion injury. Anaesthetic conditioning is a widely described strategy to attenuate ischaemia–reperfusion injury. We therefore conducted the Volatile Anaesthetic Protection of Renal Transplants-1 trial, a pilot project evaluating the influence of two anaesthetic regimens, propofol- *vs* sevoflurane-based anaesthesia, on biochemical and clinical outcomes in living donor kidney transplantation.

Methods. Sixty couples were randomly assigned to the following three groups: PROP (donor and recipient propofol), SEVO (donor and recipient sevoflurane), and PROSE (donor propofol and recipient sevoflurane). The primary outcome was renal injury reflected by urinary biomarkers. The follow-up period was 2 yr.

Results. Three couples were excluded, leaving 57 couples for analysis. Concentrations of kidney injury molecule-1 (KIM-1), *N*-acetyl-β-D-glucosaminidase (NAG), and heart-type fatty acid binding protein (H-FABP) in the first urine upon reperfusion showed no differences. On day 2, KIM-1 concentrations were higher in SEVO [952.8 (interquartile range 311.8–1893.0) pg $mmol^{-1}$] compared with PROP [301.2 (202.0–504.7) pg $mmol^{-1}$]. This was the same for NAG: SEVO, 1.835 (1.162–2.457) IU $mmol^{-1}$ *vs* PROP, 1.078 (0.819–1.713) IU $mmol^{-1}$. Concentrations of H-FABP showed no differences. Measured glomerular filtration rate at 3, 6, and 12 months showed no difference. After 2 yr, there was a difference in the acute rejection rate ($P=0.039$). *Post hoc* testing revealed a difference between PROP (35%) and PROSE (5%; $P=0.020$). The difference between PROP and SEVO (11%) was not significant ($P=0.110$).

Conclusions. The SEVO group showed higher urinary KIM-1 and NAG concentrations in living donor kidney transplantation on the second day after transplantation. This was not reflected in inferior graft outcome.

Clinical trial registration. NCT01248871.

Key words: biomarkers; kidney transplantation; propofol; reperfusion injury; sevoflurane

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Editor's key points

- Ischaemia reperfusion injury (IRI) may affect outcome after several types of surgery including kidney transplantation
- Anaesthetic agents may attenuate IRI to varying degrees through preconditioning, but the effect on outcome after kidney transplantation is unknown
- In this randomized study, there were some differences in early urinary biomarkers of kidney injury between patients receiving Sevoflurane or propofol-based anaesthesia
- There were no significant differences in outcome between groups, but the study may have been underpowered to detect this

Anaesthetic conditioning (AC) is the ability of anaesthetic agents to induce biochemical changes that may attenuate ischaemia–reperfusion injury (IRI).[1] These capacities are attributed in particular to volatile anaesthetic (VA) agents, such as sevoflurane or isoflurane, and to a much lesser extent to propofol. Depending on the timing of administration, it is defined as preconditioning (before ischaemia), perconditioning (during ischaemia), or postconditioning (directly upon reperfusion). Protective effects of AC of VA on the heart are demonstrated *in vitro*, in animal species, and in randomized controlled clinical trials.[2–4] In contrast, in kidneys the evidence for AC of VA is restricted to *in vitro* and animal work. Rats anaesthetized with VA and subjected to renal IRI showed reduced concentrations of plasma creatinine and cytokines, reduced pro-inflammatory leucocyte infiltration, and reduced histological renal necrosis compared with rats anaesthetized with pentobarbital or ketamine.[5] In mice, anaesthesia with isoflurane led to reductions of neutrophil, macrophage, and lymphocyte infiltration after renal IRI compared with pentobarbital anaesthesia.[6]

The presumed mechanism of renal AC with VA is complex and involves several pathways in different cell types.[7] In renal tubular cells, VA exposure will lead to translocation of phosphatidylserine (PS) to the outer leaflet of the plasma membrane. This externalization of PS inflicts release of transforming growth factor-β (TGF-β) in neighbouring cells via ligation of PS receptors. Binding of TGF-β to the TGF-β receptor results in increased expression of CD-73 via nuclear translocation of transcription factor mothers against decapentaplegic homolog 3 (SMAD-3). This increased CD-73 expression increases adenosine formation. Activation of adenosine receptor (AR) then results in sphingosine kinase (SK-1) upregulation directly via hypoxic inducible factor 1α (HIF-1α) signalling or indirectly via increased interleukin (IL)-11 synthesis by activation of extracellular regulated kinase/mitogen-activated protein kinase (ERK/MAPK). SK-1 itself promotes sphinogosine-1-phosphate (S1P) synthesis. Sphinogosine-1-phosphate signalling is associated with cell survival and cell growth by activation of the S1P receptor (S1PR). Furthermore, in the immune system S1P is a regulator of T- and B-cell trafficking and is directly able to suppress the Toll-like receptor (TLR)-mediated immune response from T cells.[7]

Experiments on pulmonary epithelial and endothelial cells suggest that the trifluoronated carbon groups of VA are responsible for the anti-inflammatory and immunomodulatory effects.[8]

To date, the choice of anaesthetic agent in renal transplantation is mainly based on the individual preference of the attending anaesthetist or based on local institutional protocols. Given that IRI is inevitable in organ transplantation and AC might be an effective way to reduce IRI, we designed the Volatile Anaesthetic Protection Of Renal transplants (VAPOR) trial, which is a two-step study looking at the effect of two commonly used anaesthetic agents on renal outcome in kidney transplantation. As the first step, we report here the results of the VAPOR-1 trial, a pilot study in which propofol-based anaesthesia was compared with sevoflurane-based anaesthesia in living donor kidney transplantation (LDKT). We have chosen LDKT for the first step because it is a homogeneous and reproducible model of kidney transplantation. It provided us with a maximally controllable research setting, with optimal kidneys and similar ischaemia times. Given that the rate of failure defined as delayed graft function (DGF) is low (<5%) compared with renal transplantation with kidneys from deceased brain death donor (15–40%) or deceased circulatory death donor (40–80%), we considered VAPOR-1 a proof of concept.

We hypothesized that sevoflurane-based anaesthesia is able to induce renal AC and thereby reduces post-transplant renal injury reflected by lower concentrations of kidney injury biomarkers compared with propofol-based anaesthesia.

Methods

Study design and population

This prospective, randomized controlled pilot project was conducted at the University Medical Centre Groningen between September 2010 and October 2014. The Institutional Review Board approved the study protocol (METc 2009/334), which was conducted in adherence to the Declaration of Helsinki, and registered with ClinicalTrials.gov: NCT01248871. Inclusion criteria were as follows: age $\geq$ 18 yr, donation of the left kidney, and written informed consent. Exclusion criteria were as follows: ABO-incompatible transplantation, altruistic donors, and BMI $\leq$17 or $\geq$ 35 kg m^{-2}. Only left kidneys were included because the gonadal vein was used for venous sampling upon reperfusion. The follow-up period was 2 yr.

Sample size calculation

Owing to the lack of available data in this investigational area, it was difficult to perform an adequate sample size calculation based on published data. However, we did perform a sample size calculation based on clinical urinary kidney injury molecule-1 (KIM-1) concentrations in living donors in our own centre (Nijboer WN, Leuvenink HGD, Ploeg RJ. University Medical Centre Groningen, unpublished data) to give us some idea of group size.

In a one-way ANOVA with suspected means of 100, 150, and 200 ng ml^{-1} and a common SD within a group of 90 ng nl^{-1}, we would have needed 17 patients per group (at a significance level of 0.05 and a power of 80%). Based upon this calculation, we decided to include 20 couples per group.

Randomization

Randomization was performed by the attending anaesthetist using sealed envelopes. Sixty donor–recipient couples (120 patients in total) were equally assigned to one of the following groups: PROP, propofol for donor and recipient, control group; SEVO, sevoflurane for donor and recipient, anaesthetic pre- and postconditioning; and PROSE, propofol for donor and sevoflurane for recipient, anaesthetic postconditioning. Owing to negative results in animal experiments, we did not include a fourth group (SEPRO, sevoflurane for donor and propofol for recipient, anaesthetic preconditioning).[5]

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