

Review

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Review

Donor Conditioning and Organ Pre-Treatment Prior to Kidney Transplantation: Reappraisal of the Available Clinical Evidence

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Abstract: Therapeutic measures aimed at optimising organ function prior to transplantation - whether by conditioning the donor after determination of brain death or by improving organ preservation after kidney removal - have the potential to enhance outcomes after transplantation. The particular advantage is that, unlike any optimised immunosuppressive therapy, a positive effect can be achieved without side effects for the organ recipient. In recent years, several such measures have been tested in controlled clinical trials on large patient cohorts following kidney transplantation. Hypothermic pulsatile machine perfusion in particular has become the focus of interest, but interventions in the donor prior to organ removal, such as the administration of low-dose dopamine until the start of cold perfusion as an example of conditioning antioxidant therapy, and therapeutic donor hypothermia in the intensive care unit after brain death confirmation have also significantly reduced the frequency of dialysis after transplantation with far less effort and cost. With regard to a favourable effect on graft survival in the long-term, the database for all procedures is less clear and controversial. The aim of this review article is to re-evaluate the available clinical evidence on the basis of the large multicentre controlled trials, which have also significantly influenced later meta-analyses, and to assess the significance for use in routine clinical practice.

Keywords: cold ischaemia; delayed graft function; donor conditioning; dopamine; graft survival; hypothermic machine perfusion; kidney transplantation; organ preservation; primary nonfunction; randomised controlled trial; therapeutic hypothermia

Introduction

Transplantation is the best possible treatment for patients with end-stage renal disease. However, there is a considerable discrepancy worldwide between the need and availability of organs for transplantation. Therefore, considerable efforts have been made in recent decades to make optimal use of the limited resource of transplantable kidneys through sophisticated allocation algorithms and improved logistics to limit ischaemia times. Advances in immunosuppressive therapy have steadily increased success rates after kidney transplantation [1,2]. The quality of donor kidneys can also be improved by therapeutic intervention prior to transplantation [3]. This includes organ-protective measures that start already in the intensive care unit (ICU) after confirmation of brain death, including the administration of conditioning drugs, and the use of machine perfusion (MP) after removal of the kidneys from the donor organism. During recent years a number of large controlled clinical trials (RCT) on this topic have been published in high ranked journals. While the administration of steroid boluses to reduce post-ischaemic renal transplant failure or intravenous levothyroxine for stabilisation of cardiac function failed to demonstrate any effectiveness [4,5], therapeutic donor hypothermia [6], donor pre-treatment with low-dose dopamine [7] and hypothermic pulsatile MP each reduced the need for dialysis after transplantation. However, the effects on long-term graft survival are less clear. An improvement in initial graft function is

undoubtedly a success. Nevertheless, a detailed examination of the data leaves several questions unanswered that are related to the ambivalence of the study endpoint - delayed graft function (DGF) - and must be discussed in terms of cost and benefit. The aim of this article is to take another critical look at the available evidence.

Postoperative Dialysis as a Clinical Endpoint

The requirement of dialysis immediately after transplantation was investigated in all the controlled clinical trials discussed in this article. In the hypothermia and MP studies, the use of only one postoperative dialysis in the first week after transplantation was taken to assess efficacy according to the internationally recognised definition of DGF, while the need for repeated postoperative dialyses until the onset of graft function was considered the primary endpoint in the dopamine study. The advantage of the latter definition is that it is less susceptible to an indication bias. To date, there are no generally applicable indication criteria for dialysis after transplantation. Its indication is often based solely on the post-operative state of the recipients, including their laboratory values, and is subject to the subjective judgement of the treating nephrologist. Singular dialysis is not necessarily synonymous with initially impaired graft function. For example, a single dialysis may only be required to correct an early postoperative fluid or electrolyte imbalance (hyperkalaemia). Repeated postoperative dialysis as an endpoint, on the other hand, more accurately reflects graft dysfunction. The duration of postoperative dialysis dependency has been shown to correlate with an unfavourable prognosis for the graft [10], while a single dialysis leads to comparable long-term results to kidneys that have resumed function without postoperative dialysis [11].

Therapeutic Donor Hypothermia

In 2015, the results of a large multicentre intervention study of therapeutic donor hypothermia were published [6]. Circulatory stable organ donors after determination of death according to neurological criteria were randomly assigned to one of two targeted temperature ranges: 34 to 35 °C (hypothermia) or 36.5 to 37.5 °C (normothermia). Initiation and maintenance of therapeutic hypothermia in the ICU took place over a period of 16 to 24 hours after the determination of brain death. Four adverse events occurred in the organ donors: one episode of cardiac arrhythmia and one episode of systemic hypertension in the hypothermia group, and two episodes of cardiac arrest prior to organ removal in the normothermia group. Since the mean time interval in the USA from the determination of brain death to the start of cold perfusion is around 24 hours [12], no additional costs were incurred. The study intervention was conducted in two organ donor regions in the USA and examined the incidence of DGF in the recipient institutions where the transplantation took place. The trial was terminated prematurely after an interim analysis showed highly significant efficacy after the enrolment of 370 of the planned 500 donors. 302 had at least one kidney transplanted, and 566 recipients had complete outcome data. DGF occurred in 79 of 280 (28.2%) transplant recipients from the hypothermia group and in 112 of 286 (39.2%) from the normothermia group ($P=0.008$). The favourable effect of induced hypothermia was particularly pronounced in the subgroup of extended criteria donors (ECD) with a DGF rate of 31.0% compared to 56.5% in the control group ($P=0.003$).

In retrospect, we were also able to observe a positive effect of a lower core body temperature in the organ donor on the initial graft function after kidney transplantation in the database of the randomised dopamine study coordinated by us. However, we found no advantage with regard to the graft function rate in the long-term course [13]. This was later confirmed by the investigators of the hypothermia study who overall failed to demonstrate a significant graft survival benefit 1-year after transplantation ($p=0.15$). Surprisingly, there was a small survival advantage of 4% in kidney transplants from standard criteria donors (SCD) only, which just reached the significance level [14]. However, this finding was put into perspective by a more recent RCT conducted by the same group [15]. This trial involved a total of 934 kidney transplants exclusively from SCD. There was no difference in postoperative dialysis frequency, 17% in the hypothermia group vs. 18% in the normothermia group, with an adjusted odds ratio (OR) for DGF of 0.92 (95% confidence interval [CI] 0.64-1.33, $P=0.66$).

Dopamine

Why donor dopamine? As early as the late 1990s, retrospective observational clinical studies from our own centre indicated that kidney transplant recipients from a donor who had received dopamine in the ICU prior to organ removal had better early function after transplantation and required less postoperative dialysis [16,17]. At that time, the administration of low-dose dopamine to supposedly stabilise renal function in the ICU was still widespread. Controlled clinical data have now clearly demonstrated that dopamine is not able to prevent or shorten acute renal failure in critically ill patients [18]. On the contrary, as outlined in a 2003 review article by Holmes and Walley, entitled “Bad medicine: low-dose dopamine in the ICU”, even renal doses of dopamine can cause unfavourable side effects, worsen splanchnic oxygenation, impair the gastrointestinal tract, negatively affect the endocrine and immunological systems and weaken respiratory drive [19]. All of these side effects are mediated via adrenergic or dopaminergic receptors. For this reason, dopamine has now been largely eliminated from intensive care therapy.

The data situation described above has certainly made the general acceptance of donor dopamine for conditioning the kidneys in the ICU prior to transplantation more difficult, but does not argue against its efficacy. Due to a pleiotropic mechanism of action, protection is mediated via dopamine’s antioxidant property rather than a receptor effect. Under the conditions of cold preservation, oxidative stress occurs, among other things through the degradation of haemoproteins (cytochrome P450) with the resulting release of catalytic iron ions [20,21]. Oxidative stress in turn leads to a release of calcium from intracellular stores and an increased influx of calcium from the extracellular space [22,23]. Calcium must be pumped out of the cell interior to maintain cellular homeostasis. This consumes energy-rich phosphates that cannot be regenerated under cold conditions. Calcium accumulation inside the cell also leads to damage to the mitochondrial membrane with the consequence of an increased leakage of oxygen radicals into the cytosol. A vicious circle is set in motion until the mitochondrial membrane potential finally collapses [24]. It has been shown that dopamine slows down the vicious circle of intracellular calcium accumulation and ATP loss due to its reducing properties and can thus delay cold ischaemia damage. The prerequisite is that dopamine has been accumulated in sufficient concentration in the intracellular space prior to cold preservation [25].

Dopamine and all natural and synthetic catecholamines have a benzene ring hydroxylated in the 3,4 ortho position. As a result, the molecule has reducing properties and can absorb free electrons from oxygen radicals, which are increasingly produced under cold preservation conditions. Conformational change by dihydroxylation in the 3,5 meta-position, on the other hand, leads to a loss of the reducing effect, which also completely abrogates protection against cold preservation injury. The N-terminal residue, which distinguishes the various vasoactive derivatives from each other, determines their affinity to the adrenergic or dopaminergic receptors. N-acylation of dopamine increases lipophilicity and significantly improves the efficacy of protection. Derivatives such as N-octanoyl-dopamine (NOD) would be advantageous for the conditioning of donors because they no longer have a haemodynamic effect [26]. However, they are not authorised in humans. Dopamine therefore represents a compromise to a certain extent, as dopamine has the least vasoactive side effects compared to other catecholamines at a given equivalent dose. For these side effects the brain-dead donor needs to be closely monitored in the ICU to prevent circulatory destabilisation.

In a prospective randomised clinical trial, organ donors received either a standard dopamine infusion of 4 µg/kg*min until cross-clamping or no infusion after the confirmation of brain death. Donors were included if they were circulatory stable with only a minimal dose of noradrenaline (<0.4 µg/kg*min) and had a serum creatinine <1.3 mg/dl on admission to the ICU. Kidneys were allocated to recipients centrally by Eurotransplant on the basis of waiting time and HLA matching. The primary endpoint was the need for more than 1 dialysis after transplantation. The study evaluation was conducted in 60 European transplantation centres. Donor dopamine significantly reduced the need for repeated dialyses (24.7 vs. 35.4%, P=0.01). A post-hoc analysis revealed that the effect of donor organ conditioning was quantitatively greatest in the subgroup with the longest cold ischaemia (>17 h), which fits well with the underlying molecular mechanism of action. In addition,

renal function and freedom from dialysis 1 week after transplantation correlated with the duration of the dopamine infusion [7]. Both the primary endpoint and the 5-year graft survival rate showed some saturation kinetics after an application time of slightly more than 7 hours [27] - consistent with the aforementioned experimental findings that dopamine's protection depends on its diffusion into the cell interior [25], which in turn is a time-dependent process. While no statistical effect on long-term graft survival could be demonstrated in the intention-to-treat analysis, there was a significant survival benefit when dopamine was administered for longer than 7 hours (90.3% vs. 80.2%, log rank $P=0.04$, after censoring for death with functioning graft). Due to circulatory side effects, the dopamine infusion had to be terminated prematurely in 15% of the donors. However, none of the donors were destabilised, and the function of their kidneys after transplantation was absolutely comparable to that of the control group that had not received a dopamine infusion.

Hypothermic Pulsatile Machine Perfusion

The European multicentre study on hypothermic pulsatile MP, published in the *N Engl J Med.* in 2009 [8], has given the method a worldwide boost, although the data situation has remained ambiguous due to non-negligible shortcomings in the conduct and analysis of the study. In this study, the primary endpoint, a reduction in DGF from 26.5 to 20.8%, was only borderline significant ($P=0.05$) when one-sided statistical tests were used in the analysis. This was justified by the design of a formal paired study, in which the kidneys from one donor each were randomly assigned to MP or static cold storage. However, the paired design and thus the approach of a paired statistical analysis can also be questioned, as the performance of both kidneys of a donor is often not equally distributed on both sides. In addition, the vascular anatomy (aberrant vessels), including the quality of surgical organ harvesting, often differs significantly between the right and left sides. More importantly, the endpoint of the study was determined in two different recipients with individually different risks of requiring dialysis after transplantation and, as mentioned above, does not necessarily reflect graft function. In fact, no difference in creatinine clearance at 14 days was observed (42 vs. 40 ml/min, $P=0.25$). One point really worthy of criticism is that the preservation method was changed in 25 donors (4.6%) for technical reasons (aortic patch too small/too many renal arteries for connection to the MP device) contrary to randomisation. Taking in account the relatively small study effect (reduction of postoperative dialysis incidence by 5.7%), this led to a non-negligible distortion in the allocation of kidneys to treatment. Assuming that a comparable number of kidneys in the control arm had also not allowed vascular connection to the MP device, the above-mentioned protocol violation resulted in approximately 9% of the kidneys that were statically cold stored having a more complicated vascular anatomy compared to the MP arm. The accumulation of kidneys with more complicated vascular anatomy likely also increased complexity of the surgical vascular anastomoses in the control arm and may have biased the study results in favour of MP. As is well known, despite the attempt to adjust for the number of renal arteries, a bias cannot be eliminated by statistical adjustments in the data analysis. It is noteworthy that in the control arm, primary non-function (analysed as a secondary endpoint) was recorded in 4.8% of cases, while the rate in the machine perfused kidneys was 2.1%. The difference was not considered significant in the original publication with a P -value of 0.08. However, in contrast to the statistical analysis of the primary endpoint, this time an unpaired test was applied. With a paired Fisher's exact test, the P -value of 0.04 is even below the significance level determined for the primary endpoint. This would make the European multicentre study the only randomised trial to date that has demonstrated a clinical effect of MP on initial graft failure. A later meta-analysis on this issue, including the European multicentre study, was unable to show any influence on primary non-function [28]. In this context, it should be mentioned that about one third of early graft losses after kidney transplantation is due to technical failure or problems with the vascular anastomoses, as large registry data from the Netherlands and the UK consistently show [29]. Another notable omission is that 7 donor pairs in whom technical failure of the MP occurred after randomisation, as shown in the study flowchart in the original publication, were excluded from the analysis. The researchers do not specify whether these kidneys were still transplantable - and if so - had initial or delayed graft function or failed. In the event that failure of MP was in fact a major

adverse event of the trial intervention, a data analysis according to the intent-to-treat principle would be appropriate. Given one additional kidney assigned to MP had failed the primary trial outcome would have missed the statistical significance level also in the paired analysis.

The investigators of the European multicentre study report a favourable effect of MP on the 1-year function rate of the transplanted kidneys (94 vs. 90%, log rank $P=0.04$). The quantitative difference of 4% (91 vs. 87%) was also statistically significant when analysing the 3-year function rates [30]. After 1 year, the survival curves were parallel without further divergence. Thus, in purely mathematical terms, 67.5% of the survival advantage after 3 years can be attributed to the difference in initial non-function. Two meta-analyses, including the largest European multicentre study at the time, were unable to demonstrate a significant effect on graft survival [28,31]. Another meta-analysis, which only considered studies published after 2010, found no effect at all [32]. Nevertheless, in their conclusion, the authors of the Cochrane meta-analysis [28] made the following statement: "...There is strong evidence that hypothermic MP has a positive impact on transplant survival in both the short and long term, in both DBD and DCD grafts. This is to be expected given previous research has shown the DGF is associated with higher rates of kidney loss..." There may be subgroups that particularly benefit from MP, e.g., kidneys from donors after cardiac death or from brain-dead ECD. In a separate analysis embedded in the European multicentre study the focus was specifically on kidneys from the latter donor category [33]. There was a comparable reduction in DGF of 7.7%, from 29.7 to 22%. At the same time, the incidence of initial non-function was 4-fold higher in the controls (12 vs. 3%, $P=0.04$). This resulted in a 1-year graft survival advantage in favour of MP of 92.3 vs. 80.2%, $P=0.02$. However, in 5.5% of the ECD, the perfusion method had also been switched contrary to the initial randomisation. The researchers' conclusion that recipients of ECD kidneys particularly benefited from MP therefore remains limited against the background of the selection bias inherent in the study already discussed.

The bold prediction by Tingle et al. [28] cited above has since been relativized by a more recent US American trial from 2023 [9]. This 3-arm RCT, the largest in number to date, aimed at comparing MP with or without intended donor hypothermia versus hypothermia alone, found no difference in 1-year graft survival. The Kaplan-Meier survival curves were exactly superimposed in all 3 groups, although in the two MP groups the DGF rate was significantly reduced by 8 and 11% respectively - with a comparable dialysis frequency in the control group as in the European study, in which the body temperature was not lowered before organ removal. The study was originally intended to show that donor hypothermia is not inferior to MP. Therefore - when compared with the European multicentre study - the result was unexpected due to the even greater reduction in the primary endpoint by MP. Even in the recent study, the treatment of the kidneys was not always carried out in accordance with the randomisation. However, unlike in the European multicentre study, protocol violations contrary to randomisation, which occurred for technical or organisational reasons in 27% of the kidneys allocated to MP, were handled in the analysis according to the intention-to-treat principle, so that a selection bias was avoided. It should be emphasised that the control group in the current study was not affected by an increased incidence of primary non-function.

The trial by Malinoski et al. [9] was designed and conducted as an open study. After assignment to the preservation method, no other specifications were made at the transplantation centre level with regard to the organisational procedure and timing of transplantation. Therefore, two important questions arise, namely whether the selected study endpoint DGF was able to specifically differentiate early graft dysfunction and whether the complex MP logistics justify the general application of MP in the light of the available findings. Both questions are naturally closely linked [34]. It is noticeable that the machine perfused kidneys were only transplanted after a longer duration of cold ischaemia of 2.5 hours on average [9]. Due to the large number of transplants performed in each study arm, it can hardly be assumed that the difference occurred by chance. Rather, in the recent past the view has prevailed that kidneys at the MP tolerate longer cold ischaemia, so that organisational processes in the transplant centres could be improved or even nocturnal transplants avoided [32]. This view has yet to be tested against evidence-based criteria and is based solely on small, monocentric and retrospective observational studies [35–38]. In a post-hoc analysis, the

investigators of the European multicentre study examined the effect of MP in strata of cold ischaemia. They found that cold ischaemia time remained an independent risk factor for DGF even in machine perfused kidneys, both in kidneys from brain-dead donors, including ECD donors, and in donors after circulatory death [39]. These data suggest that hypothermic MP is unlikely to significantly protect the renal graft from injury caused by prolonged cold ischaemia.

Basically, it is well conceivable that the idea of an increased ischaemia tolerance in machine perfused kidneys meant that transplants were performed under less time pressure. The acceptance of a somewhat prolonged cold ischaemia at the transplant centre level also allows a longer dialysis time immediately before the operation. The question therefore arises as to whether the recipients of a machine perfused kidney were dialysed for longer before the operation than control subjects. A consecutively lower serum creatinine and BUN may have led to a postponement of dialysis treatment prior to the onset of graft function, thereby reducing its incidence in the MP group. In such a scenario the more frequent use of a postoperative dialysis in the controls is not necessarily an indication of impaired early graft function after transplantation, in particular when only a singular dialysis was performed. If there was indeed a statistical correlation between dialysis time before and dialysis incidence after surgery, it should be analysed whether the effect of MP on a reduced DGF rate is maintained with a comparable preoperative dialysis time. Additional sensitivity analyses using the need for >1 postoperative dialysis as an outcome measure, including the duration of DGF, could be helpful to better detect graft dysfunction. Data on renal function, in particular calculations of eGFR, e.g., on postoperative day 7, could enable an objective assessment of whether MP has actually improved early function after kidney transplantation. The proposed post-hoc analyses are feasible with reasonable effort, as the required data are routinely collected from each transplant recipient. They could demonstrate the efficacy of MP beyond the reduction of an ambiguous treatment-related endpoint that is susceptible to indication bias.

Summary

All of the procedures discussed in this review article have reduced the dialysis frequency after kidney transplantation in large multicentre studies. The clinical benefit for a broad applicability of therapeutic donor hypothermia has been somewhat tempered by recent controlled data, as it appears to be effective in reducing the incidence of dialysis only in kidneys from ECD [6,15]. Nor has it been shown that the method improves graft function. The advantage is that therapeutic hypothermia can be carried out easily and without side effects in brain-dead organ donors in the ICU before organ removal and does not incur any additional costs.

Donor dopamine, as an example of antioxidant organ conditioning prior to transplantation, led dose-dependently with the infusion-time to improved renal function and greater freedom from dialysis during the first week after transplantation in a randomised clinical trial [7]. When analysed on intention-to-treat, donor dopamine had no significant effect on graft survival, but was associated with a survival benefit after 5 years if the dopamine infusion was administered for >7 hours until cross-clamp [27]. Based on experimental and clinical data, dopamine's protection against cold ischaemia injury is not limited to the kidneys [40,41]. Dopamine also improved the survival of heart transplant recipients from multi-organ donors included in the dopamine trial [42]. Dopamine was largely eliminated from intensive care therapy due to its ineffectiveness in stabilising renal function in the critically ill. Due to the negative press of the substance in intensive care medicine, it is not very likely that the promising approach of donor conditioning with dopamine will be pursued further clinically and experimentally in order to clarify unanswered questions.

In contrast, hypothermic pulsatile MP in particular has attracted a worldwide interest. At the same time, the available data has been accepted somewhat prematurely, which has already led to a widespread use of the method in clinical practice. In the meantime, it has become clear that MP has no effect on graft survival after kidney transplantation. It also remains unclear whether MP actually improves early renal function. The European multicentre study was unable to demonstrate any effect on renal function 14 days after transplantation [8], and more recent controlled data have not yet convincingly demonstrated this either [9]. This is in parts due to the ambivalence of the chosen

primary study endpoint, which corresponds to the internationally used definition of DGF, but is extremely susceptible to external influences and therefore not specific for an assessment of early graft function. Additional sensitivity analyses, which could easily be carried out at low expense, could provide evidence-based information on whether the considerable logistical and cost effort associated with MP really justifies the routine use of the procedure.

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