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Associate Editor of *World Journal of Transplantation*, Frank JMF Dor, MD, PhD, FEBS(Hons), FRCS, Consultant Transplant Surgeon and Clinical Lead for Transplantation, Hammersmith Hospital, Imperial College Healthcare NHS Trust, W120HS, London, United Kingdom. frank.dor@nhs.net.

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OPINION REVIEW

Pre-emptive live donor kidney transplantation-moving barriers to opportunities: An ethical, legal and psychological aspects of organ transplantation view

David van Dellen, Lisa Burnapp, Franco Citterio, Nizam Mamode, Greg Moorlock, Kristof van Assche, Willij C Zuidema, Annette Lennerling, Frank JMF Dor

ORCID number: David van Dellen 0000-0002-5695-6939; Lisa Burnapp 0000-0002-3757-4003; Franco Citterio 0000-0003-0489-6337; Nizam Mamode 0000-0001-8549-9098; Greg Moorlock 0000-0001-5493-0463; Kristof van Assche 0000-0002-8368-1993; Willij C Zuidema 0000-0001-5055-080X; Annette Lennerling 0000-0001-9729-8701; Frank JMF Dor 0000-0003-2448-7362.

Author contributions: van Dellen D, Lennerling A and Dor FJMF designed the research study; van Dellen D wrote the manuscript; all authors performed the research, have rad and approved the final manuscript

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David van Dellen, Department of Renal and Pancreas Transplantation, Manchester University NHS Foundation Trust, Manchester M13 9WL, United Kingdom

David van Dellen, Department of Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, United Kingdom

Lisa Burnapp, Nizam Mamode, Department of Transplantation, Guy's and St. Thomas' NHS Foundation Trust, London SE1 9RT, United Kingdom

Franco Citterio, Department of Surgery, Renal Transplantation, Catholic University, Rome 00153, Italy

Greg Moorlock, Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom

Kristof van Assche, Res Grp Personal Rights & Property Rights, University of Antwerp, Antwerp 2000, Belgium

Willij C Zuidema, Departments of Internal Medicine, Erasmus Medical Centre, Rotterdam CE 1015, Netherlands

Annette Lennerling, The Transplant Centre, Sahlgrenska University Hospital, Gothenburg S-413 45, Sweden

Annette Lennerling, Institute of Health and Care Sciences, The Sahlgrenska Academy, University of Gothenburg, Gothenburg S-405 30, Sweden

Frank JMF Dor, Imperial College Renal and Transplant Centre, Hammersmith Hospital, London W2 1NY, United Kingdom

Corresponding author: David van Dellen, FRCS, MD, Surgeon, Department of Renal and Pancreas Transplantation, Manchester University NHS Foundation Trust, Oxford Road, Manchester M13 9WL, United Kingdom. david.vandellen@mft.nhs.uk

Abstract

Live donor kidney transplantation (LDKT) is the optimal treatment modality for end stage renal disease (ESRD), enhancing patient and graft survival. Pre-emptive

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LDKT, prior to requirement for renal replacement therapy (RRT), provides further advantages, due to uraemia and dialysis avoidance. There are a number of potential barriers and opportunities to promoting pre-emptive LDKT. Significant infrastructure is needed to deliver robust programmes, which varies based on socio-economic standards. National frameworks can impact on national prioritisation of pre-emptive LDKT and supporting education programmes. Focus on other programme's components, including deceased kidney transplantation and RRT, can also hamper uptake. LDKT programmes are designed to provide maximal benefit to the recipient, which is specifically true for pre-emptive transplantation. Health care providers need to be educated to maximize early LDKT referral. Equitable access for varying population groups, without socio-economic bias, also requires prioritisation. Cultural barriers, including religious influence, also need consideration in developing successful outcomes. In addition, the benefit of pre-emptive LDKT needs to be emphasised, and opportunities provided to potential donors, to ensure timely and safe work-up processes. Recipient education and preparation for pre-emptive LDKT needs to ensure increased uptake. Awareness of the benefits of pre-emptive transplantation require prioritisation for this population group. We recommend an approach where patients approaching ESRD are referred early to pre-transplant clinics facilitating early discussion regarding pre-emptive LDKT and potential donors for LDKT are prioritized for work-up to ensure success. Education regarding pre-emptive LDKT should be the norm for patients approaching ESRD, appropriate for the patient's cultural needs and physical status. Pre-emptive transplantation maximize benefit to potential recipients, with the potential to occur within successful service delivery. To fully embrace preemptive transplantation as the norm, investment in infrastructure, increased awareness, and donor and recipient support is required.

Key Words: Pre-emptive; Kidney transplantation; Living donor; Ethics; End-stage renal disease

Core Tip: Live donor kidney transplantation (LDKT) is the optimal treatment for end stage renal disease (ESRD), particularly pre-emptively, prior to requirement for renal replacement therapy. There are a number of potential barriers and opportunities to promoting this: (1) National frameworks; (2) Health care providers and transplant programmes; (3) Societal norms/cultural expectations; (4) LKDT donors; And (5) Patients with ESRD. We recommend an approach where: Patients approaching ESRD are referred early; potential donors are prioritized; education regarding pre-emptive LDKT should be the norm; pre-emptive transplantation maximize benefit to potential recipients. Investment in infrastructure, increased awareness, and donor and recipient support is required.

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INTRODUCTION

Live donor kidney transplantation (LDKT) remains the optimal modality for treatment of end stage renal disease (ESRD). It has been demonstrated to provide improvements in both graft and patient survival in comparison to transplantation from a deceased donor[1]. Pre-emptive transplantation, which occurs prior to the recipient's requirement for dialysis, has demonstrated improvements in patient and graft survival in

comparison to implantation after the commencement of dialysis[2,3]. The cumulative benefit of pre-emptive live donor transplantation should provide tangible benefits. However, there remains a paucity of data to support this attitude to transplantation, although it appears logical based on existing data to promote this form of live donor transplantation.

The mechanisms for improved outcomes, both in terms of patient and graft longevity, with pre-emptive transplantation are not well understood although it is hypothesized that it may be a consequence of reduced co-morbidity burden due to avoidance of uraemia and dialysis, or due to improved patient selection[4]. It is also thought that the greater residual renal function improves patient resilience to a major intervention and an attenuated immune response in the recipient[4-6].

There is concern as to the timing of pre-emptive transplantation in general. There remain international variations with respect to the timing of deceased organ transplantation. However, historically pre-emptive transplantation is considered when the glomerular filtration rate (GFR) approaches ESRD to optimize both patient and graft survival[7]. Recent studies have postulated, however, that this should occur shortly prior to the need to initiate dialysis, when uraemic symptoms become prevalent, although the data for this remains equivocal in randomized trials[8-10]. This will usually occur at a GFR between 7-10 mL/min, albeit with consideration regarding the rate of decline of renal function[11]. However, the optimal timing ultimately for transplant is currently recommended to be shortly or a few months prior to the need to commence dialysis[12,13].

The debate over pre-emptive transplantation is relevant almost exclusively to renal transplantation. This is because of the evolution of durable renal replacement therapy (RRT), which allows more structured planning of transplant timing[14]. This hasn't been mirrored in other organ transplants where pre-emptive approaches, by necessity, remain the norm, due to the absence of viable organ replacement therapies. The ethical considerations regarding pre-emptive transplantation are relevant almost exclusively in the context of renal transplantation, where these choices exist.

Pre-emptive transplantation is, however, not without controversy, as there remain significant challenges to the provision of an equitable and sustainable service for all service users, without priority being given to certain aspects of the transplant process, particularly at the expense of deceased donor transplantation. These reflect potential challenges in both the systematic provision of pre-emptive live donor transplantation due to obstacles from health care providers (HCP) as well as societal challenges. The potential impact on both donor and recipient, particularly with extended exposure to immunosuppression and its associated deleterious effects also require consideration. The transplant community has historically engaged with and provided innovative solutions to ethical dilemmas that expand the boundaries of clinical practice, but there remains a paucity of data that unequivocally demonstrates a solid foundation for pre-emptive transplantation. These studies are urgently needed to provide robust support for engagement with this process, as the current patient load and clinical pressures mandate continued engagement in pre-emptive transplantation.

LDKT, which has evolved and now largely underpins the success and progression of the majority of transplant programmes, has to strike the balance between success, whilst minimizing acceptable risk to both the transplant donor and recipient. This has particularly resonated with increased awareness of the potential long term risk to organ donors[15,16].

This has inevitably increased focus on providing sustainable, safe LDKT programmes that maintain public confidence in the robustness and safety of the entire process. There is a requirement for accountability to both the profession and society as a whole.

There are therefore a number of potential barriers and opportunities with respect to promoting and evolving pre-emptive LKDT, both individually and as a systematic process. We classify and characterize these, specifically focusing on opportunities with respect to the various stakeholders in the process: (1) National Frameworks; (2) HCP and transplant programmes; (3) Societal norms/cultural expectations; (4) LKDT donors; and (5) Patients with ESRD (including family and social networks).

Each of these groups has distinct areas of concern and influence in ensuring access to pre-emptive LDKT, and these will be examined in more detail. We particularly aim to examine factors influencing and understand the potential cause of variability in access and adoption of pre-emptive transplantation.

NATIONAL FRAMEWORKS AND SOCIETY

The delivery of a successful pre-emptive living donor programme requires an established and efficient transplantation infrastructure. There is significant variability internationally in the maturity of living donor programmes, predominantly linked to prevailing national socioeconomic standards[17]. This results in varying priorities with respect to emphasis for development and progression. This is particularly true with increasing emphasis on the potential and deliver of paired exchanged and immunologically complex transplants, which require the existence of significant infrastructure and clinical input.

There is also a requirement supporting primary care facilities for early identification of patients with evolving chronic kidney disease (CKD), to allow identification and optimization of patients increasing the chances of achieving transplantation pre-emptively. There are a number of methods to improve cohesion between referring centres and the transplant team to facilitate this. This is largely coupled with education programmes for patients, their relatives and HCP's, which highlight the benefit of live donation, and particularly pre-emptive transplantation[18,19]. There is also a need for local and national regulatory authorities to provide infrastructural and financial support to allow these initiatives to flourish.

This approach has to be balanced against the confines of limited capacity in most programmes and should not be seen to adversely affect other aspects of the service delivery by impinging on the capacity of local systems to provide unrelated aspects of the programme for patients who may not have the benefit of pre-emptive live donor options to enable RRT.

HCP/INDIVIDUALIZED TRANSPLANT PROGRAMMES

HCP's have to balance competing concerns in delivering safe and efficient healthcare in modern society. These include the overriding objectives of beneficence (doing good for the individual patient), and justice (ensuring fairness for all patients) that may require medical interventions across a wide variety of services and significant ethical considerations[20].

This is particularly relevant in a financially contracting health economic model, which is currently evident in both Europe and North America. In addition, there are significant shifts in national health care priorities in the developed world, with an aging population and an emphasis on treatment and support of this as well as a focus on services with high priorities or profiles. This includes a culture where there has been, and remains, an expectation for continued improvements in areas such as cardiovascular and cancer services. This has to be balanced against the challenges of designing, innovating, and continuing to deliver high quality transplantation services.

LDKT has the added overriding responsibility of minimising risk to the potential donor. This has been focused by recent data regarding long term risks that has resulted in significant re-evaluation of the donor pool[15,16]. This is particularly highlighted in pre-emptive LDKT, where the urgency and benefit of transplantation may not yet be obvious.

The potential significant recipient benefit of pre-emptive live donor transplantation is countered by the need to ensure that this does not impact on investment, both in terms of resources and finance in the live donor pathway as a whole for all patients, ensuring continued equity of access to services. It is particularly important that access to transplantation for those who are already on dialysis cannot be compromised. These concerns are already being addressed in the development of strategies to promote LDKT in the United Kingdom amongst other countries[21]. These highlight the need to maximize patient benefit by ensuring that all suitable recipients have appropriate resources invested in their care. This should ensure that no other patients in 'conventional' work-up (particularly those who have commenced dialysis) are perceived to have been disadvantaged. In addition, it highlights the importance of embedding the principle of 'transplant first' initiative in clinical practice for all potential LDKT recipients. This initiative focuses on increasing patient transition to transplantation prior to the need for dialysis[22].

Data demonstrates inequity in access to all transplant services amongst varying population groups. These are particularly prevalent across geographical distribution in ethnic minorities and potential recipients with socioeconomic deprivation in both North America and Europe[23,24]. This is once again further evident when potential barriers to access of live donation services are characterized[25]. This demonstrates that

a significant barrier to pre-emptive live donor transplantation may develop along both ethnic and socio-economic boundaries, and appropriate education needs to be embedded as a preventative measure within the healthcare community as a whole[19,26].

There are also regional variances both within national and international programmes with respect to referral for transplantation by nephrologists and this is mirrored in the context of pre-emptive transplantation[27,28]. There are multiple contributing factors, including whether the potential recipient is receiving treatment in a dedicated transplant centre, coupled with the attitude of the referring nephrologist. There have been suggestions that there is a lack of consistency in the practice of 'transplant first' by referring nephrologists[29]. This in turn may result in unacceptable delays in referral for transplant assessment, and the subsequent lost opportunity for pre-emptive transplantation.

It could also be postulated, although this remains controversial, that in areas where practice or remuneration is linked to the volume of patients on dialysis, that there may be a conscious or unconscious bias on the part of the nephrologist with respect to referral for LDKT. This is due to the potential impact of loss of patients or finance, although this requires further clarification. There are data to support this worrying finding, though from North America[30]. This could potentially be counteracted by a provision of financial incentive to the referring physician with preferential options for transplant follow up to ease the financial obstacles to potential referral for pre-emptive LDKT.

It has also been shown that patients receiving pre-emptive transplants have significantly better socio-economic conditions and higher education levels[8,22]. The onus is therefore on HCP's to ensure that these potential barriers are overcome by highlighting potential pre-emptive live donor options to less advantaged groups of patients with ESRD, and improving education and access to information to promote these work streams. There should also be attempts to promote early identification and referral to allow timely donor screening and workup. This could remove significant temporal barriers and improve the equality of access to transplantation.

SOCIETY

Society may provide potential barriers that are an extension of those faced by HCP's in provision of high quality care. However, there remains a susceptibility to the cultural attitudes and norms of society. The transplant community is required to identify and confront these challenges to ensure equity of access to all services. These challenges are not unique to deceased or live donor, or more specifically, pre-emptive transplantation but may be exacerbated by the unique challenge that the latter provides.

The emergence of data regarding long term live donor safety has provoked significant debate amongst HCP's regarding its acceptability[15,16,30]. There is the on-going challenge of ensuring non-maleficence whilst supporting the acceptability and progression of treatment options and healthcare as a whole. The balancing of these two aims requires significant ethical debate. However, HCP's are required to balance these concerns with the individual patient that they are treating rather than the utilitarian challenge of driving progression or overcoming limitations in health care. It remains imperative that initiatives such as 'transplant first' as well as live donation are promoted to ensure optimal patient outcome. However, the corollary to this is to ensure that HCP's pastoral role ensures that patients, and in this scenario particularly donors, have their long-term health protected and preserved during this process. This is best evidenced by the commitment to donor follow up life long, or even prioritisation of donors with subsequent ESRD to transplant options in national programmes[31].

There remain significant ethnic disparities in access to both deceased and LDKT[32,33]. These, on the whole, reflect socioeconomic inequalities and ultimately impacts as longer waiting times and decreased frequency of live donation proceeding due to a shortage of suitable and willing donors. Factors identified include both identification and recruitment of live donors as well as subsequent conversion of potential donors to actual donors[34]. This has a further impact when including the fact that the pool of deceased donors translates into patients from ethnic minorities having a prolonged wait time in this context. Pre-emptive LDKT is unlikely to prosper in this scenario. It is therefore essential that education programmes continue to focus on live donor promotion within these communities, relying on both formal systems as well as more individualised perspectives if appropriate. The success of formal education programmes has been well documented[25,26,35].

These challenges are further highlighted in the context of pre-emptive LDKT. The time critical nature of performing pre-emptive LDKT means that any potential delays, as previously highlighted, impact significantly on the ability of ethnic minorities to benefit from pre-emptive LDKT.

The ethnic and socio-economic barriers are mirrored in certain cultural environments, and particularly those with religious influence, that impact on the ability of kidney donation to proceed and therefore proportionately affect pre-emptive LDKT. Transplantation, and particularly deceased organ donation remain controversial in certain religious and cultural environments, particularly Judeo-Islamic faiths, where the focus on preservation of the integrity of the physical body after death is predominantly considered sacrosanct. This occurs despite official support for organ donation by religious leaders[36]. This in turn has fuelled conservative attitudes to transplantation in general within these communities. The reduced rates of live donation, due to religious views, mirror those seen with socio-economic deprivation, and in turn are likely to impact on proceeding to LDTK in a timely fashion, although this context remains poorly characterised.

The final societal barrier predominantly concerns potential financial impact, particularly to the donor in terms of lost income. This is well described in the context of overall LDKT, but also applies to pre-emptive transplantation[36,37]. A recent survey identifying patient perceptions, and predominantly focused on barriers to pre-emptive transplantation, identified financial concerns as a significant stressor[37]. This corroborates previously reported findings that patients who received a LDKT had a significantly higher annual income, thereby again potentially initiating bias against those from lower socio-economic groups. There was also increased out of pocket costs for both donor and recipients. All of these factors can create disparities in access to transplantation based on financial means. The onus is on society as a whole to provide greater support for LDKT mechanisms to progress. This is particularly because of the well-proven financial benefits of successful transplantation to society as a whole, both in terms of on-going health care costs on RRT and the opportunity for successful recipients to return to employment. This may be overcome in situations where, although controversial in certain environments, reimbursement of live donors is facilitated at an appropriate level to act as an incentive[38]. This is counteracted by the obvious financial benefits of avoiding RRT and improved recipient longevity, both of which provide significant benefit to the national health economy.

DONOR FACTORS

Donor willingness to engage in the LDKT is integral to the success of any durable live donor programme. The legal frameworks that govern the process aim to protect the donor and minimise potential opportunities for solicitation of organs. In addition, it is difficult to extrapolate emotions or barriers in donor to coming forward for pre-emptive LDKT, as each case will have individualised circumstances, challenges and opportunities.

As previously noted, recent data highlighting higher than previously perceived risk associated with live donation has had a significant impact on counselling and consent processes for organ donation. Although the relative risks remain very low, this may impact on donor willingness to volunteer[15,16]. This is especially pertinent in light of the fact that, unlike any other procedures, a donor nephrectomy is being performed on a patient with no pre-existing pathology, thereby strengthening the desire to ensure optimal outcomes[15]. The primary obligation of responsible clinicians caring for the donor is their outcome, thereby aiming to exclude any emotional pressures between donor and recipient or medical factors that may promote pre-emptive transplantation in the latter. This must obviously be in the context that, in a significant proportion of cases, there will already be a strong emotional bond between the donor and recipient pair.

The consent process should inform donors of potential risk, particularly based on these recent data, which may result in donor dropout, although this risk requires further clarification[39,40]. This is particularly relevant in extended criteria donors, where pre-existing comorbidities, and particularly Diabetes Mellitus and hypertension, may further heighten perceived or relative risk for the donor based on recent evidence. HCP's may also be resistant to pre-emptive LDKT if they feel that it is unwise to place any donor in a position of perceived or higher than expected risk when the potential recipient may not yet demonstrate all of the severe physical and psychological effects of ESRD, even in situations where voluntary consent has been established.

Within the context of pre-emptive LDKT, live donation also has to demonstrate that the earlier time frame for donation doesn't adversely affect the potential donor in any way. This is especially pertinent in light of the potential time pressures to achieve donation prior to the potential recipient receiving dialysis. This should not allow any unnecessary acceleration or dereliction in live donor work up, which may in turn impact compromise donor's long-term safety. However, an additional value to the entire process may be the improved psycho-social benefit to the potential donor by providing additional advantage to their recipient at an earlier time point.

Recipients receiving pre-emptive LDKT may not have experienced dialysis, increasing the risk of non-adherence and this may be mirrored in donors where the vicarious emotional distress of a family member or friend on dialysis has not yet been experienced[41]. This may act as a barrier to donors who are not yet aware of the potential for the patient with ESRD to undergo significant physical and emotional stress once dialysis commences. In addition, similar circumstances may occur if the transplant subsequently fails due to either technical or immunological reasons[41]. Previous data demonstrate short-term transient deteriorations in mental health that recovers over months[42,43]. These findings could be extrapolated to pre-emptive donors where the mitigating emotions of a recipient experiencing dialysis are not experienced vicariously by the donor.

Pre-emptive transplantation may, conversely, also provide improved convenience for the potential donor because the process, once commenced, is not halted to allow deterioration of renal function to a predetermined threshold. This approach may streamline the process of donor assessment and progression to donation. This prevents potential delays for the recipient commencing dialysis, thereby placing the potential donor's life on hold. There is a need for careful pragmatism of what best fits the convenience of the donor with balancing the ideal timing to maximize the longevity of the graft for the recipient's benefit. Definitive processes will need to be defined to ensure the timing of the transplant procedure, between all involved parties.

TRANSPLANT RECIPIENTS

There are a number of pre- and post-surgical factors that result in variation in access to and outcomes for pre-emptive transplantation for patients with ESRD. This has to be countered with the view that any exposure to dialysis has a detrimental effect both on patient and graft survival. Longer pre-transplantation dialysis exposure is an independent risk factor for progressively higher risk of all cause transplant failure from any cause, including death[44].

Pre-emptive transplantation provides the best option for patients with ESRD in terms of durable RRT. However, there may be barriers to ensuring adequate access and acceptability of this option. The predominant cause for these is socioeconomic or societal barriers, as previously noted. However, there also needs to be consideration regarding optimisation of the potential recipient and ensuring that no medical contraindications exist to preclude successful outcome. A recent meta-analysis and position statement highlighted a number of potential medical barriers that might impact on this process[11].

In addition, concern remains regarding a perceived lack engagement with the possibility of pre-emptive LDKT, mimicking the features seen in non-adherent patients after transplantation[41]. This is predominantly seen in young recipients and largely occurs as the result of patients who have not yet experienced the deleterious effects on quality of life that are characteristic after commencing dialysis treatment[45]. However, there remains an absence of robust data to substantiate this, and this phenomenon may therefore be overestimated, as does the potential harmful effects of prolonged immunosuppression exposure[11,46]. There is, however, evidence to support that quality of life on dialysis is lower than patients with less advanced chronic kidney disease, the general population and individuals suffering from other chronic medical conditions[47-49].

These factors highlight the importance of education for the potential transplant recipient regarding the benefits of pre-emptive transplantation and to manage the expectations of the recipients with respect to their experiences around the time of transplant. This may also include focus on the benefits of transplantation and associated experiences in comparison to RRT. This should include recognition of the importance of quality-of-life benefits for patients, which may supersede metrics such as graft and patient longevity, which predominate medical outcome measures. However, the former remain difficult to quantify and provide valid reproducibility

across various patient groups, although there are data to support their value and current potential for improvement in uptake[50-52].

Another barrier to pre-emptive LDKT is the success and progression of dialysis treatment in terms of quality of life and durability for the patient, particularly intensive or nocturnal home haemodialysis. However, this method of RRT has shown conflicting benefits in terms of improvements in quality of life whilst LDKT has overwhelming favourable evidence[53]. In addition, mortality data regarding intensive haemodialysis is equivocal whilst transplantation again has shown significant and sustainable benefit, particularly in the context of pre-emptive transplantation[54]. However, in certain circumstances, consideration also needs to be given to the fact that intensive or home haemodialysis may provide a better option than further attempts at pre-emptive transplantation. This is particularly valid in situations such as recurrent focal segmental glomerulosclerosis, which may have caused recurrent disease in a previous transplant, necessitating delays and careful consideration of the benefit of further transplantation[54]. However, this approach should be seen as an exception rather than the norm.

CONCLUSION

The overwhelming responsibility of HCP's is to ensure beneficence whilst minimising the chances of harm. Pre-emptive LDKT, if timed appropriately, maximises benefit to the potential recipient. However, within the context of modern healthcare it remains vital that both the individual and the entire service's requirements are fulfilled. This provides a number of barriers and opportunities that may prevent access to full adoption of this process.

These include a number of fundamental areas that underpin this process and that have been evaluated in some detail relevant to both the individuals involved in the process, namely the HCP's, potential donor and recipient but also the system and society into which they are integrated.

The progression of pre-emptive LDKT requires significant investment into education programmes earl in the ESRD pathway, to ensure continued empowerment of individuals to represent and promote their interests. Transplantation has the benefit of well-informed patients who have chronic involvement in health care prior to requiring interventions due to the chronic nature of ESRD. There is therefore the opportunity to promote initiatives such as 'transplant first' but, more importantly, to particularly focus on LDKT, thereby potentially increasing pre-emptive numbers. This will require earlier discussion of these options with patients by HCP's.

Pre-emptive transplantation offers the potential benefit of improving patient outcome. By improving knowledge of the entire transplant community improving access to this initiative will have a significant impact on transplant programmes worldwide. Further work is also needed to understand potential differences in attitudes to pre-emptive transplantation between recipients receiving their first organ and those who may have had the experience of previous transplants.

This group therefore has a number of specific recommendations: Patients approaching ESRD should be directed to a pre-transplant clinic and not be prepared for dialysis as the norm. The discussion regarding pre-emptive live donation should occur and be the norm. This should be supported with live donor advocates and active promotion of pre-emptive LDKT in a multidisciplinary setting. On this basis, approaching and preparing potential donors for LDKT should be prioritised.

Education regarding pre-emptive LDKT should be the norm for patients approaching ESRD. This should be appropriate for the patient's cultural needs and physical as well as psychosocial status. Adequate resources are required at both a regional and national level to allow pre-emptive LDKT to be facilitated.

Transplantation requires an approach that promotes live donation, with specific focus on the benefit of a pre-emptive approach. Societal and transplantation structures need to be designed with this aim prioritised. This is particularly important in view of some of the cultural and societal challenges that occur regarding deceased donation, which in turn heighten the importance of live donation. There should be focus on early education and increased acceptance of this beneficial approach for prospective donors and recipients and HCP's. This will ensure the best use of valuable donated live donor organs and, in turn, improved outcomes for recipients.

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MINIREVIEWS

Does steroid-free immunosuppression improve the outcome in kidney transplant recipients compared to conventional protocols?

Ahmed Aref, Ajay Sharma, Ahmed Halawa

ORCID number: Ahmed Aref 0000-0003-4184-3883; Ajay Sharma 0000-0003-4050-6586; Ahmed Halawa 0000-0002-7305-446X.

Author contributions: Halawa A selected the topics for the work, providing expert advice on our work and the final editing of the manuscript; Sharma A contributed the supervision of the scientific presentation of the data collection together with the quality evaluation of the data presented; Aref A designed the work, collected the data and wrote the manuscript.

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Ahmed Aref, Department of Nephrology, Sur hospital, Sur 411, Oman

Ajay Sharma, Department of Transplantation, Royal Liverpool University Hospitals, Liverpool 111, United Kingdom

Ahmed Halawa, Department of Transplantation, Sheffield Teaching Hospitals, Sheffield S5 7AU, United Kingdom

Corresponding author: Ahmed Halawa, FRCS (Gen Surg), MSc, Surgeon, Department of Transplantation, Sheffield Teaching Hospitals, Herries Road, Sheffield S5 7AU, United Kingdom. ahmed.halawa@sth.nhs.uk

Abstract

Steroids continue to be the cornerstone of immune suppression since the early days of organ transplantation. Steroids are key component of induction protocols, maintenance therapy and in the treatment of various forms of rejection. Prolonged steroid use resulted in significant side effects on almost all the body organs owing to the presence of steroid receptors in most of the mammalian cells. Kidney allograft recipients had to accept the short and long term complications of steroids because of lack of effective alternatives. This situation changed with the introduction of newer and more effective immune suppression agents with a relatively more acceptable side effect profile. As a result, the clinicians have been contemplating if it is the time to abandon the unquestionable reliance on maintenance steroids in modern transplantation practice. This review aims to evaluate the safety and efficacy of various steroid-minimization approaches (steroid avoidance, early steroid withdrawal, and late steroid withdrawal) in kidney transplant recipients. A meticulous electronic search was conducted through the available data resources like SCOPUS, MEDLINE, and Liverpool University library e-resources. Relevant articles obtained through our search were included. A total number of 90 articles were eligible to be included in this review [34 randomised controlled trials (RCT) and 56 articles of other research modalities]. All articles were evaluating the safety and efficacy of various steroid-free approaches in comparison to maintenance steroids. We will cover only the RCT articles in this review. If used in right clinical context, steroid-free protocols proved to be comparable to steroid-based maintenance therapy. The appropriate approach should be tailored individually according to each recipient immunological challenges and clinical condition.

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Core Tip: Prolonged steroid therapy was associated with many complications that ranged from cosmetic changes to life-threatening increase in cardiovascular risk profile. The utilisation of antibody induction, together with calcineurin inhibitors maintenance immune suppression, had markedly reduced the incidence of acute rejection. The improved rate of acute rejection encouraged different transplant centres to adopt new steroid-free protocols, especially in fragile cases with multiple comorbidities. Variable steroid-free approaches were tried. We aim to explore the safety and efficacy of various steroid-free protocols by comparing each different modality with the conventional triple immune suppression.

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INTRODUCTION

Kidney transplantation continues to prove itself as the best treatment modality for patients with end stage renal disease (ESRD). Kidney transplantation not only improves patient survival, but enhances the quality of life and psychological well-being for those patients[1-3]. The introduction of potent induction protocols utilizing antibodies targeting T-cell receptors together with the availability of effective maintenance immune-suppressive agents has dramatically improved the first-year allograft outcome. On the other hand, the long-term outcome did not show similar improvement, mostly secondary to long term side effects of prolonged immune suppressive medications[4,5]. Steroids have been used since the early days of organ transplantation to prevent the loss of transplanted organs by the recipient immune system[1,4]. The usage of steroids came with a high cost of complications that includes cosmetic changes, metabolic disturbances, skeletal complications, growth affection in pediatric patients and increase risk of cardiovascular morbidity and mortality[1,4]. Variable approaches were adopted by different transplant centers to decrease the burden of steroid side effects either by steroids withdrawal or total steroid avoidance[5]. Discontinuation of steroids after few days of transplantation is called early steroid withdrawal (ESW), while late steroid withdrawal (LSW) implies holding steroids after weeks or months after the transplantation. On the other hand, if steroids were not administered at all, this is called steroid avoidance[1]. Several studies were performed to evaluate the efficacy of various steroid minimization approaches which showed favorable short-term outcome. However, long term outcome is still not validated[5]. In the following sections we shall explore the safety and efficacy of various steroid-minimization approaches namely, steroid avoidance, ESW, and LSW in kidney transplant recipients.

EPIDEMIOLOGY

There has been a continuous rise in the number of patients suffering from ESRD, which was translated into a growing number of kidney transplant recipients. In the United States, the number of kidney transplant recipients increased by 106.6% during the period from 2000 to 2017. Furthermore, Kidney transplant recipients in the United States reached more than 222000 by the end of 2017, representing about 30% of all cases treated by renal replacement therapy[6].

A meta-analysis of randomized controlled studies proved the efficacy of induction protocols in lowering the risk of acute rejection (AR) among kidney allograft recipients in the first year allowing utilization of less aggressive maintenance immune-suppression[7]. Data from the United States published in Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) annual report showed that more than 70% of the kidney transplant recipients received induction *via* a T-cell depleting agent (namely rATG or alemtuzumab), and less commonly the non-depleting agent basiliximab (chimeric anti-CD25) was used as the induction agent, while transplantation without induction became relatively uncommon for both adult[8] and pediatric recipients[9].

Early results from randomized controlled studies (RCS) showed a significant improvement in cardiovascular risk profiles in transplant recipients with steroid-free protocols[10,11]. On the other hand, there was an increased risk of AR, which did not significantly affect the first and five-years patient and graft outcome[11]. Nevertheless, long term benefits and consequences of steroid avoidance were not confirmed[10,11].

STEROID-FREE PROTOCOLS IN SPECIAL POPULATIONS

There is currently a generalized consensus that steroid-free protocols should be considered in kidney transplant candidates after careful evaluation of possible benefits and expected risks of each patient individually[1,10]. In 2009 Kidney Disease: Improving Global Outcomes Transplant Work Group have suggested using induction protocols utilising one of the lymphocytes depleting agents in case of high-risk of AR[12]. High-risk transplantation is considered in the presence of one or more of the following risk factors[12]: (1) Afro-American ethnicity; (2) Old aged donor; (3) Increased number of human leukocyte antigens (HLA) mismatch; (4) High panel reactive antibody (PRA); (5) Presence of donor-specific antibody (DSA); (6) Prolonged cold ischemia time; and (7) Blood group (ABO) incompatible transplantation.

Steroid free protocols have long been used for low immunological risk situations. However, the safety and efficacy of steroid minimization in high immunological risk transplantation was not adequately addressed in clinical trials[13].

Steroid withdrawal in African American transplant recipients

Kidney transplantation in African American population was traditionally considered a procedure with high immunological risk due to the associated higher incidence of AR and chronic allograft nephropathy as well as the inferior graft outcome compared to other ethnic groups[14]. Several studies have shown that African American recipients have immune hyper-responsiveness, more HLA polymorphisms, in addition to several important cytokine polymorphisms[13].

The short and intermediate-term outcome after ESW were evaluated in a few studies that showed acceptable results in the term of patient and graft survival[14,15]. However, these studies were retrospective in nature and included a small number of patients and control.

Data from the United Network of Organ Sharing (UNOS) transplant registry was utilized to perform the most extensive comparative study comparing the outcome of 5565 black kidney transplant recipients who had their steroids withdrawn by the time of hospital discharge after the transplantation versus a matched 5565 black recipients who continued on steroid maintenance therapy[13]. Ten years patient and allograft outcomes were comparable in both groups[13].

Steroid withdrawal in kidney re-transplantation

There is a growing number of patients who are being relisted and re-transplanted after the failure of their kidney allograft[16]. Candidates for kidney re-transplantation are more likely to suffer from significant co-morbid conditions (secondary to prolonged immune suppression, pre-transplant comorbidities, the original renal disease, and ageing itself)[17].

Many of the existing co-morbidities are likely to benefit from ESW. On the other hand, re-transplantation candidates are likely to have antibodies to HLA that are expressed on the donor's kidney, and they will be progressively sensitised with each failed allograft experience. Therefore, they are more prone to poor graft outcome secondary to immunological causes unless potent immune suppression was implemented[16,17]. Few studies focused on the outcome of ESW in the setting of kidney retransplantation[18,19]. The available studies showed an acceptable short and intermediate-term patient and graft outcome provided that the recipient received

induction therapy with a T-cell depleting agent[18,19].

Steroid withdrawal in sensitised kidney transplant recipients

Kidney transplant candidates are called sensitised if they have anti-HLA antibodies which increase the risk of rejection. Therefore, such patients used to be considered at high immunological risk and steroids were a cornerstone in their maintenance immune suppression[20]. Sensitised patients may have antibodies to HLA antigens secondary to previous blood transfusion, pregnancy, or prior failed transplants[20]. The analysis of data obtained from OPTN/UNOS showed that maintenance steroid therapy was associated with increased risk of death with functioning graft in kidney allograft recipients with peak PRA less than 30%. However, maintenance steroid usage was associated with improved death censored graft survival and without negative impact on patient survival for recipients with peak PRA more than 60%[20].

Steroid withdrawal in ABO incompatible kidney transplantation:

ABO incompatibility was once a contraindication for kidney transplantation as it was associated with hyperacute rejection and graft loss[1]. The introduction of desensitisation protocols has changed this concept over the past few decades making ABO incompatible (ABOi) kidney transplantation relatively a realistic option[21]. Nevertheless, potent maintenance immune suppression utilising triple agents was commonly used to achieve excellent patient and graft survival[22]. Several centres investigated the challenge of early withdrawal[23,24] and the late withdrawal of steroids[25,26]. All these studies showed an acceptable patient and graft outcome in addition to the avoidance of long-term complications of steroids. However, all these studies involved a small number of cases. Well organised studies still required to investigate the outcome of a large number of cases over prolonged time of follow up to consolidate the cost-effectiveness of steroid sparing in the setting of ABOi kidney transplantation[24-26].

Steroid withdrawal in transplantation after glomerulonephritis

Treatment of most of the primary glomerulonephritis includes the use of steroids to achieve and maintain remission[2]. Recurrence of glomerulonephritis post-transplantation is a feared situation as it indicates a worse allograft survival[27]. Large data registry showed that maintenance steroid therapy has no statistical significance on patient and allograft outcome in recipients with recurrent glomerulonephritis[28,29].

Steroid withdrawal in older patients

Kidney transplant recipients older than 60 years are commonly defined as elderly patients[30,31]. The prevalence of ESRD in older people is substantial[6]. There is growing evidence that kidney transplantation in elderly suffering from renal failure has a better outcome than other modalities of renal replacement therapy. However, the ideal immune suppression protocol in elderly recipients remains undefined[30]. The innate and adaptive immune responses are blunted in the elderly. Furthermore, elderly recipients are more vulnerable to infection, malignancy and metabolic diseases which makes the reduction of maintenance immune suppression a sensible option[30,31]. There are no RCT evaluating ESW in the elderly. Nevertheless, retrospective data from a small number of patients showed a similar outcome in elderly recipients when compared to younger recipients in the setting of ESW[31].

Steroid withdrawal in paediatrics

Despite that pediatric recipients are liable to the same adverse effects of immune-suppressive medications expressed in adults; they are also vulnerable to unique complications like the affection of growth[32,33]. Factors associated with catch up growth includes recipients less than six years old, well-functioning allograft and steroid-free immune suppression[32,33]. Several reports concluded that steroid-free protocols in pediatric patients would eliminate the long-term complications of steroids without a negative impact on patient or graft survival[34,35].

DATABASES

Aiming to explore the data evaluating the impact of steroid-free protocols on the outcome in the field of kidney transplantation, we performed an extensive search of the online database using MEDLINE, SCOPUS, as well as Liverpool University library

e-resources. Relevant articles obtained through our search were included.

Supplementary search approaches

After completing the initial electronic database search, grey literature and hand search of the table of contents of the relevant scientific journals were started, aiming to identify additional relevant data. Any related citations were checked against the previously collected data obtained from the electronic search to avoid articles duplication.

Selection of the articles included

The final collection of articles obtained from the search of the electronic database, grey literature, as well as a hand search of the related journals were screened initially *via* the title of the article. The next step was evaluating the abstracts of the selected papers accepted by the initial search. Finally, the complete manuscripts of the approved articles were reviewed to decide the final studies included in this review.

Assessment of articles quality

While preparing this literature review, a wide range of variability in methodology and study design was encountered. Therefore, we decided to include only randomized controlled trials (RCT). RCT are one of the most reliable tools for evaluating the safety and effectiveness of medical intervention. However, not all RCT present a reliable result[36]. Low-quality RCT with poor methodology may carry a significant bias which will result in misleading conclusions[36]. Therefore, RCT articles included in our study will be subjected to a further evaluation process utilizing the modified Jadad scale[37].

The Jadad scale (which sometimes called the Oxford quality scoring system) is a scoring tool created in 1996 to estimate the methodological quality of RCT[38]. The original scale was composed of 5 questions which evaluate the randomisation, blinding and accountability of all cases, including the dropouts. The modified Jadad scale is composed of 8 questions which assess the points covered by the original scale in addition to inclusion and exclusion criteria evaluation, assessment of adverse effects, and statistical analysis evaluation as illustrated in Table 1[37].

The RCT are scored between 0 (which is the lowermost quality) and 8 (the uppermost quality). Scores between 4 and 8 mean the articles considered of good to excellent quality, while articles with score 0 to 3 are of poor quality[37]. A data extraction sheet was prepared for summarizing the essence of the included studies as well as the quality assessment of the study as presented in Table 2.

DISCUSSION

Despite being one of the oldest available immune suppressants, steroids continue to play a central role in the modern immune suppression protocols. Steroids can be used as an induction agent, in maintenance immune suppression as well as in the treatment of rejection episodes[1,2]. Most mammalian cells have cytoplasmic receptors for steroids that explains the potent and diffuse anti-inflammatory and immunosuppressive actions on both innate and adaptive immune systems[1]. Common steroid-induced complications include osteoporosis, impaired glucose metabolism, hypertension, dyslipidemia, growth retardation in children, weight gain, cataract, poor wound healing, cosmetic changes, mood disturbance, and insomnia[1,3].

Steroid-free protocols

The use of steroids in the field of transplantation was considered indispensable for many decades. However, the better understanding of immune response, improved techniques of tissue typing and cross-matching, together with the introduction of potent and relatively safe immune suppressants have potentiated the trend of steroid-free immune suppression[1,2]. Various approaches for steroid-free do have comparable AR in the first-year post-transplantation in comparison to conventional protocols. However, the long-term patient and graft outcome remains controversial[1-3].

RCT on steroid-free protocols

The published RCT papers were involving adult and pediatric recipients, as mentioned in Table 2. Steroid-free protocols were associated with a better metabolic profile, an improved cardiovascular risk profile and lower total costs of medical care (owing to fewer expenses on the management of steroid-induced complications).

Table 1 The modified Jadad scale[37]

Item evaluated	Finding	Score
Was the study described as randomized?	Yes	+ 1
	No	0
Was the method of randomization appropriate?	Yes	+ 1
	No	- 1
	Not described	0
Was the study described as blinded? (double-blind with score 1; single-blind with score 0.5)	Yes	+ 1
	No	0
Was the method of blinding appropriate?	Yes	+ 1
	No	- 1
	Not described	0
Was there a description of withdrawals and dropouts?	Yes	+ 1
	No	0
Was there a clear description of the inclusion/exclusion criteria?	Yes	+ 1
	No	0
Was the method used to assess adverse effects described?	Yes	+ 1
	No	0
Were the methods of statistical analysis described?	Yes	+ 1
	No	0

The randomised controlled trials are scored between 0 (which is the lowermost quality) and 8 (the uppermost quality). Scores between 4 and 8 mean the articles considered of good to excellent quality, while articles with score 0 to 3 are of poor quality[37]. A data extraction sheet was prepared for summarizing the essence of the included studies as well as the quality assessment of the study as presented in Table 2.

Pediatric recipients have an additional advantage which is the improvement of growth parameters with a remarkable catch-up growth, especially in pre-pubertal recipients. On the other hand, some studies showed a mild but real risk of increased incidence of early AR which did not affect the patient and graft survival for up to 5 years of follow up[11].

In middle east, the patients carry the burden of significant co-morbidities (*e.g.* diabetes mellitus, hypertension, and ischaemic heart disease) the assumed risk of steroids outweigh the mildly increased risk of AR (which was documented by most of the listed RCT to be mild and responding to treatment with no long term effects on patient and graft survival).

Other study modalities on steroid-free protocols

Many studies of different modalities were evaluating the effect of steroid-free approaches not only in adults and pediatrics but also in other special population recipients like African American, elderly, ABOi recipients and after kidney re-transplantation. Retrospective analysis of long term follow up (up to 15 years post-transplant) showed significantly lower rates of steroid associated complications. Furthermore, there was a significant improvement in patient and allograft survival[39,40].

Recipients with special medical considerations like elderly, patients with high immunological risk and those with a history of glomerulonephritis in native kidneys were traditionally kept on oral steroids indefinitely assuming that steroid-free protocols carry a detrimental effect on the patient and allograft outcome. Surprisingly, most of the studies focused on these special population groups showed a favorable outcome with steroid-free protocols. Nevertheless, a well-designed RCT still awaited to confirm these observations.

Essential considerations with steroid-free approaches

Adopting any of the available steroid-free protocols should be carefully designed

Table 2 Summary of randomised controlled trials articles

Ref.	Cases included	Aim of the study	Results and conclusions	Modified Jadad score
van Sandwijk *et al*[43], 2018	186 patients with follow up for about 2 yr	To compare ESW (day 3 post-transplant), triple therapy with low dose tacrolimus and standard tacrolimus dose triple therapy	All groups showed no statistically significant differences in patient survival, allograft survival, incidence of acute rejection and eGFR Steroid withdrawal group has better cardiovascular risk profile and lower rates of infection	6
Andrade-Sierra *et al*[44], 2016	71 patients with follow up for 12 mo	To compare the impact of ESW (day 5 post-operative) with maintenance steroid use.	One-year graft survival was comparable (87% versus 94% in controls) Steroid free group has higher eGFR and better blood pressure control with fewer anti-hypertensive drugs (8% versus 50%; $P < 0.001$).	4
Nagib *et al*[45], 2015	428 patients with follow up for 66 ± 41 mo	To investigate long term outcome of ESW (steroids used for three days only) in living donor kidney allograft recipients	Steroid avoidance in low immunological risk recipients was both safe and effective using basiliximab induction Long term follow-up showed decreased total cost with steroid-free protocol despite comparable immune suppressant cost, mostly secondary to lowering the burden of chronic comorbidities related to steroid use	4
Thierry *et al*[46], 2014	131 patients were followed for 30 mo	To evaluate the impact of SA in comparison to LSW	At the end of the study period, 32.4% of steroid avoidance patients and 51.7% of steroid withdrawal group were receiving oral steroids There were no significant differences in kidney functions, proteinuria, or documented rejection between both groups	6
Ponticelli *et al*[47], 2014	139 patients with follow up for 12 mo	Evaluating the short-term impact of LSW (3 mo post-transplantation)	Treatment failure was noted in 14.7% of steroid withdrawal group compared to 2.8% in the control group NODAT was reported in 13.2% of steroid withdrawal group compared to 1.9% in the control group	6
Krämer *et al*[48], 2012	421 patients with follow up for three years	The outcome of two different steroid-free regimens in comparison to the conventional triple immunosuppressive therapy	Despite the increased risk of early acute rejection with steroid-free protocols, the long-term patient and graft survival were comparable Steroid free regimens were associated with a better cardiovascular risk profile	6
Thierry *et al*[49], 2012	222 low risk, de novo kidney transplant recipients with follow up for 6 mo	Evaluation of the short-term outcome of SA after 500 mg methylprednisolone + IL-2 receptor antibody induction in comparison to conventional maintenance steroids	The short-term outcome in the form of patient survival, graft survival, the incidence of BPAR and GFR were similar in both groups. However, SA was associated with a lower incidence of CMV infection (12.5% versus 22.7%, $P = 0.045$)	6
Gheith *et al*[50], 2011	100 patients with a median follow up of twelve months	Assessing the cost-benefit of ESW (3 d post-transplant) in living donor kidney allograft recipients	Despite the comparable immunosuppressant costs, steroid avoidance was associated with significantly lower total costs by the end of the first year after transplantation The higher costs associated with steroid use was attributed to the cost of management of steroid-related comorbidities	4
Sandrini *et al*[51], 2010	96 patients were followed for up to 4 yr	To compare the efficacy of ESW (day 5) versus later withdrawal after 6 mo of transplantation	Both strategies had comparable patient survival, graft survival, allograft function and percentage of successful withdrawal ESW was associated with less wound healing complications (4% *vs* 21%, $P = 0.02$). On the other hand, LSW was associated with a lower incidence of acute rejection at 12 mo (30% *vs* 48%, $P < 0.04$), and at 48 mo (33% *vs* 53%, $P < 0.03$)	5
Delgado *et al*[52], 2009	37 patients with follow up for five years	Evaluating ESW (7 d post-transplant) effect on the development of de novo donor-specific anti HLA antibodies (DSA)	ESW was not associated with increased risk of development of de novo DSA compared with conventional steroid maintenance protocol	5

Sandrini *et al*[53], 2009	148 patients were followed for the first 15 d	To measure the impact of ESW on wound healing in comparison to maintenance steroids in patients receiving sirolimus therapy	ESW was associated with a significantly lower rate of wound healing complications (18.8% *vs* 45.6%, $P < 0.0004$)	3
Woodle *et al*[11], 2008	386 patients with follow up for five years	To compare the outcome of ESW (7 d post-transplant) with low dose chronic corticosteroid therapy	ESW was associated with increased risk of BPAR mostly corticosteroid-sensitive Banff class 1A rejections. However, the five-year allograft survival and function were similar in both groups Steroid withdrawal was associated with better metabolic and cardiovascular risk profiles	8
Vincenti *et al*[54], 2008	337 patients with follow up for 12 mo	Comparing the safety and efficacy of total SA ($n = 112$), ESW ($n = 115$) and standard maintenance steroid regimen ($n = 109$) in first kidney allograft recipients	The median eGFR by the end of the first year was comparable between all groups The incidence of BPAR was significantly higher with both steroid-free and early withdrawal groups compared to patients maintained on steroids Lipid profile, weight gain, and glycaemic control were better in steroid-free groups	6
Pelletier *et al*[55], 2006	120 recipients with follow up of minimum 1 yr after randomisation	To assess the impact of LSW compared to maintenance steroids	Patient and allograft survival, acute rejection rates and allograft function were similar in both groups Steroid withdrawal was associated with a significant improvement in bone density and total cholesterol levels	5
Rostaing *et al*[56], 2005	538 patients with follow up for six months	Short term outcome with a steroid-free protocol using Dac, Tac and MMF versus Tac, MMF, and corticosteroids regimen	Steroid free protocol was associated with a significant reduction in the incidence of NODAT (5.4% *vs* 0.4%, $P = 0.003$), in addition to improvement of serum total cholesterol levels No clinically significant difference detected between the two groups in the term of acute rejection or serum creatinine levels at the end of the study	6
Laftavi *et al*[57], 2005	60 patients were followed up by protocol biopsies at 1, 6, and 12 mo	Short term outcome of ESW (7 d after transplantation)	ESW was associated with significant and accelerated allograft fibrosis as proved by protocol biopsy findings. However, this did not affect the renal functions measured by eGFR	6
Vítko *et al*[58], 2005	451 low-risk recipients of first kidney allograft were followed up for 6 mo	Short term outcome of a steroid-free protocol using tacrolimus monotherapy after basiliximab induction (Bas/Tac) ($n = 153$), tacrolimus + MMF (Tac/MMF) ($n = 151$) or triple therapy of tacrolimus + MMF + steroids ($n = 147$)	Short term patient and graft survival at 6 mo post-transplantation were similar in all groups. However, the incidence of BPAR was higher in steroid-free groups [26.1% in (Bas/Tac) group, 30.5% in (Tac/MMF) group, and 8.2% in triple therapy group ($P < 0.001$)] The average creatinine clearance was higher in triple therapy group (65.3 ml/min), compared to Bas/Tac group (55.1 ml/min) and Tac/MMF group (59.4 ml/min) ($P = 0.007$)	6
Kumar *et al*[59], 2005	77 patients with follow up for 2 yr	Evaluating the impact of ESW (days 2-7) in comparison to low dose maintenance steroids	There were no statistically significant differences between both groups in all aspects (patient and allograft survival, acute rejection, metabolic profiles, and protocol biopsy findings)	5
Vanrenterghem *et al*[60], 2005	833 recipients with follow up for 6 mo	Estimating the short-term outcome of either steroid or MMF withdrawal after 3 mo of transplantation in comparison to standard triple therapy	The next 3 mo after randomisation showed a similar incidence of BPAR Steroid withdrawal group had a better lipid profile ($P < 0.001$) MMF withdrawal group had lower frequency of serious CMV infection ($P = 0.024$) and leukopenia ($P = 0.0082$)	5
Vincenti *et al*[61], 2003	83 recipients with follow up for 12 mo	Evaluating the impact of ESW (day 4 post-transplantation) in comparison to standard steroid therapy	Patient and allograft survival, the incidence of BPAR, graft function and rate of infections were similar in both groups	5
Boots *et al*[62], 2002	62 patients with a median follow up for 2.7 yr	To compare the outcome of ESW (7 d post-transplant) versus LSW (3-6 mo post-transplant)	Both groups had a similar patient and graft survival with similar acute rejection episodes. However, the incidence of NODAT was significantly lower in early withdrawal group	6

Sola *et al*[63], 2002	92 patients with follow up for 2 yr	Comparing the effect of LSW and maintenance steroids	There were no statistically significant differences between both groups in all aspects (patient and allograft survival, acute rejection, and metabolic profiles)	2
Boletis *et al*[64], 2001	66 patients with follow up for 12 mo	Short term outcome of LSW (6 mo post-transplant)	Serum creatinine levels were comparable in both groups, and none of them has rejection episode during the follow-up period Serum triglycerides, cholesterol and mean arterial blood pressure levels were also similar in both groups	4
Vanrenterghem *et al*[65], 2000	248 patients with follow up for 12 mo	Evaluating the short-term outcome of steroid withdrawal (3 mo post-transplant) in comparison to maintenance steroids.	Despite the increased incidence of BPAR in steroid withdrawal group (23% versus 14%; P = 0.008), yet the mean serum creatinine levels were comparable in both groups by the end of 12 mo follow up Steroid withdrawal was associated with a better lipid profile, blood pressure measurements and bone densitometry measurements at 12 mo	6
Matl *et al*[66], 2000	88 patients with follow up for 12 months.	To estimate the safety of LSW compared to continuation on triple therapy.	The allograft function, acute rejection rate and biopsy findings were similar in both groups LSW was associated with a significantly lower serum cholesterol level. However, no significant changes were observed in serum triglycerides or blood pressure measurements	2
Ahsan *et al*[67], 1999	266 patients were followed up for one year	The effect of LSW *vs* continuation on low dose steroid (all patients were receiving cyclosporine and MMF)	LSW was associated with better control of hypertension and lower serum cholesterol level There is an increased risk of Acute rejection among steroid withdrawal group 30.8% *vs* 9.8% only within maintenance steroid group The risk of rejection or treatment failure within the first-year post-transplantation was 39.6% in blacks versus 16% in nonblack (P < 0.001)	7
Steroid free immune suppression in paediatrics				
Höcker *et al*[68], 2019	42 paediatric patients (aged 11.2 ± 3.8 yr) were followed for 15 mo	The effect of steroid withdrawal on the recipient's blood pressure measured *via* ABPM	After 15 mo of follow up, there were no significant differences between both study groups in terms of allograft functions Steroid withdrawal was associated with better blood pressure readings as well as restoration of circadian blood pressure rhythm in 71.4% of cases versus 14.3% at baseline (P = 0.002)	6
Tönshoff *et al*[69], 2019	106 paediatric recipients with follow up for 12 mo	To estimate the short-term outcome of initiating everolimus with steroid elimination 5 mo post transplantation in comparison to conventional triple therapy	Patient and graft survival were 100% in both groups No statistically significant differences in the incidence of BPAR, proteinuria, and longitudinal growth	6
Webb *et al*[70], 2015	196 subjects with follow up for up to 2 yr	Evaluating the impact of ESW (at day 4 post-transplant) on the longitudinal growth	There was a significant and sustained growth improvement with ESW documented through the two years of follow up, especially in prepubertal children Patient and graft survival, the incidence of rejection and eGFR were comparable in both groups	5
Mericq *et al*[71], 2013	30 paediatric recipients were followed for 12 mo post-transplantation	Evaluating the effect of ESW on the longitudinal growth, body composition, and insulin sensitivity	Steroid withdrawal group showed better longitudinal growth, had lower trunk fat and improved lipid profile parameters compared to the control group	6
Sarwal *et al*[72], 2012	130 paediatric cases with follow up for 3 yr	Evaluating the safety and efficacy of total SA in comparison to low dose maintenance steroids	Complete SA was associated with improved cholesterol levels (P = 0.034) and lower systolic blood pressure readings (P = 0.017) Recipients below the age of 5 years showed a significant linear growth catch up with the steroid-free protocol, while other age groups did not show a significant growth difference over the 3 years of follow up	5

			Non-significant lower incidence of NODAT was recorded in steroid free group (1.7% versus 5.7%; $P = 0.373$) Incident of BPAR, patient survival and graft outcome were comparable between both groups	
Benfield *et al*[73], 2010	132 paediatric cases with data collected for up to 3 yr	Evaluating the outcome of LSW (6 mo post-transplantation) in comparison to low dose maintenance steroids	LSW resulted in a significant improvement of the Cushingoid facies compared to the control group The standardised height velocity was higher in the withdrawal group ($P = 0.033$) The allograft survival rate at 3 yr was higher in the withdrawal group (98.6% *vs* 84.5%; $P = 0.002$) Lipid profile, systolic and diastolic blood pressures showed no statistical differences between both groups The study was terminated prematurely due to high incidence of PTLD	6
Grenda *et al*[74], 2010	196 paediatric recipients follow up data of the first 6 mo post-transplantation	Evaluating the short-term outcome of ESW (at day 4 post-transplant)	ESW significantly improved the growth, especially in prepubertal recipients Parameters of lipid and glucose metabolism were significantly better in the withdrawal group. However, they suffered a higher incidence of infection and anaemia ($P < 0.05$ for all mentioned comparisons) Incident of BPAR, allograft function, patient and graft survival were similar for both groups	6
Höcker *et al*[75], 2010	42 paediatric patients with follow up for 2 yr after the withdrawal of steroids	Evaluating the effect of LSW (1 yr post-transplant) in comparison to maintenance steroids	LSW was associated with superior longitudinal growth ($P < 0.001$) Steroid withdrawal was associated with a significant decrease in the prevalence of metabolic syndrome, better control of blood pressure, and improved lipid and carbohydrate metabolism Patient survival, graft function and graft survival were not affected by steroid withdrawal	6

IL-2: Interleukin-2; Dac: Daclizumab; Tac: Tacrolimus; MMF: Mycophenolate mofetil; ABPM: Ambulatory blood pressure monitoring; PTLD: Post-transplant lymphoproliferative disorder; ESW: Early steroid withdrawal; eGFR: Epidermal growth factor receptor; LSW: Late steroid withdrawal; NODAT: New-onset diabetes after transplantation; CMV: Cytomegalovirus; DSA: Donor-specific antibody; HLA: Human leukocyte antigens; BPAR: Biopsy-proven acute rejection.

based on meticulous evaluation of the patient medical history, associated co-morbidities, clinical assessment, and immunological challenges. The recommendations obtained from all the listed studies include: (1) The patients should receive induction with a lymphocytic depleting agent; (2) Ensure adequate dosing of potent immune suppressants (*e.g.*, tacrolimus and mycophenolate mofetil) to compensate for the absence of steroids; (3) Regular evaluation of DSA, especially in highly sensitized recipients; (4) Repeated and timely protocol biopsy may provide a tool of early detection of AR before a clinically evident sequel; and (5) Keep a high index of suspicion for early symptoms and signs of AR.

Continuing steroid-free regimen versus initiating maintenance steroids after recovery from AR

One of the critical decisions after managing an AR episode is whether to start a low dose of maintenance steroid or to keep the recipient on his previous steroid-free protocol. The aim is to prevent a second attack of AR as it is undeniably associated with a poor allograft outcome[41,42]. The initiation of maintenance steroids seems to be associated with lower rates of AR and a slight improvement in allograft survival over the next three years of follow up, yet, it did not reach a statistical significance[41]. The most significant risk factor for developing a second AR episode was the histological pattern and severity of the first AR episode (RR = 5.6, $P = 0.001$)[41].

Based on the available data, we recommend individualizing the decision of prescribing maintenance steroids based on the histological description of AR, the

clinician clinical judgement as well as the patient preference. Steroid use is highly recommended following the management of moderate to severe AR with positive C4d staining[41].

CONCLUSION

The use of lymphocyte depleting induction agents is recommended whenever steroid-free maintenance therapy is planned. There are accumulating clinical studies which showed steroid-free protocols to be valuable in reducing drug-induced complications while keeping patient and allograft survival comparable to maintenance steroids.

Steroid-free protocols are the preferred therapy in pre-pubertal recipients to allow adequate catch-up growth. Steroid-free protocols may also be a valid option for patients with special medical considerations (*e.g.*, elderly, African American and borderline diabetics). A reasonable approach is to weigh the risk-benefit for each transplant candidate individually. Strict monitoring of recipients on steroid-free protocols is a must for early detection and management of AR. If the patient developed AR, then consider initiating lifelong maintenance steroids based on its severity.

Our article attempted to summarize the enormous scientific material covering this debatable topic, keeping in mind that no agreed recommendations or guidelines are available to date regarding any of the steroid withdrawal approaches. We concluded that an ideal steroid-free regimen remains elusive. Nevertheless, after reviewing all the presented RCT articles, we developed a strong belief that steroid-free protocols should have different shapes and forms taking into account patient variables (age, ethnicity, medical background, HLA mismatches, immunological risk stratification, *etc.*). It can offer a comparable outcome with a lower burden of associated co-morbidities.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Perioperative risk factors associated with delayed graft function following deceased donor kidney transplantation: A retrospective, single center study

Nicholas V Mendez, Yehuda Raveh, Joshua J Livingstone, Gaetano Ciancio, Giselle Guerra, George W Burke III, Vadim B Shatz, Fouad G Souki, Linda J Chen, Mahmoud Morsi, Jose M Figueiro, Tony M Ibrahim, Werviston L DeFaria, Ramona Nicolau-Raducu

ORCID number: Nicholas V Mendez 0000-0002-0507-8726; Yehuda Raveh 0000-0002-4780-2743; Joshua J Livingstone 0000-0003-0094-7504; Gaetano Ciancio 0000-0002-0269-4152; Giselle Guerra 0000-0002-4098-4652; George W Burke III 0000-0002-6888-2842; Vadim B Shatz 0000-0003-2828-8643; Fouad G Souki 0000-0003-0895-5496; Linda J Chen 0000-0002-0404-1745; Mahmoud Morsi 0000-0001-7236-6966; Jose M Figueiro 0000-0001-6290-0125; Tony M Ibrahim 0000-0002-3735-887X; Werviston L DeFaria 0000-0002-6949-741X; Ramona Nicolau-Raducu 0000-0002-1155-1866.

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Institutional review board statement: The study was

Nicholas V Mendez, Yehuda Raveh, Joshua J Livingstone, Vadim B Shatz, Fouad G Souki, Ramona Nicolau-Raducu, Department of Anesthesiology, University of Miami/Jackson Memorial Hospital, Miami, FL 33136, United States

Gaetano Ciancio, George W Burke III, Linda J Chen, Mahmoud Morsi, Jose M Figueiro, Tony M Ibrahim, Werviston L DeFaria, Department of Surgery, Miami Transplant Institute/University of Miami/Jackson Memorial Hospital, Miami, FL 33136, United States

Giselle Guerra, Division of Nephrology of the Department of Medicine, University of Miami/Jackson Memorial Hospital, Miami, FL 33136, United States

Corresponding author: Ramona Nicolau-Raducu, MD, PhD, Associate Professor, Department of Anesthesiology, University of Miami/Jackson Memorial Hospital, 1611 NW 12th Avenue, Miami, FL 33136, United States. rxn256@miami.edu

Abstract

BACKGROUND

There is an abundant need to increase the availability of deceased donor kidney transplantation (DDKT) to address the high incidence of kidney failure. Challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount.

AIM

To identify risk factors associated with delayed graft function (DGF).

METHODS

Consecutive adults undergoing DDKT between January 2016 and July 2017 were identified with a study population of 294 patients. The primary outcome was the occurrence of DGF.

RESULTS

The incidence of DGF was 27%. Under logistic regression, eight independent risk factors for DGF were identified including recipient body mass index ≥ 30 kg/m^2,

baseline mean arterial pressure < 110 mmHg, intraoperative phenylephrine administration, cold storage time ≥ 16 h, donation after cardiac death, donor history of coronary artery disease, donor terminal creatinine ≥ 1.9 mg/dL, and a hypothermic machine perfusion (HMP) pump resistance ≥ 0.23 mmHg/mL/min.

CONCLUSION

We delineate the association between DGF and recipient characteristics of pre-induction mean arterial pressure below 110 mmHg, metabolic syndrome, donor-specific risk factors, HMP pump parameters, and intraoperative use of phenylephrine.

Key Words: Delayed graft function; Outcome; Kidney transplant; Risk factors; Phenylephrine; Mean arterial pressure

Core Tip: There is an abundant need to increase the availability of deceased donor kidney transplantation to address the high incidence of kidney failure. Challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount. We delineate the association between delayed graft function and recipient characteristics of pre-induction mean arterial pressure below 110 mmHg, metabolic syndrome, donor-specific risk factors, hypothermic machine perfusion pump parameters, and intraoperative use of phenylephrine.

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INTRODUCTION

Chronic kidney disease and end stage renal disease are leading contributors to patient morbidity, mortality, and economic burden[1,2]. Kidney transplantation is the therapy of choice, with superior survival and improved quality of life over dialysis[3,4]. Regrettably, in the United States alone nearly 5000 patients perish each year while on the wait-list due to organ shortage[5]. A common strategy to minimize the ever-increasing gap between organ supply and demand is *via* expansion of criteria for acceptable donors[6,7]. These higher-risk kidney allografts, however, frequently exhibit delayed graft function (DGF), which in turn is associated with acute rejection, chronic allograft nephropathy, shorter allograft survival, and increased costs[8-10]. A clear need exists for the identification and optimization of modifiable perioperative risk factors associated with DGF[11]. Prior studies have pointed to an association between recipients' blood pressure and DGF, but conflicted on the clinical setting in which it contributes to DGF[12-15].

The aim of this analysis is to identify risk factors associated with DGF, with a particular focus on perioperative hemodynamic factors, since these can be more readily optimized to improve graft and patient outcomes.

MATERIALS AND METHODS

After approval by the institutional review board, all consecutive adult (age ≥ 18 years) patients who underwent a deceased donor kidney transplant (DDKT) at our center between January 2016 and July 2017 were identified. Recipients of multi-organ

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allografts were excluded, and the medical records of the remaining 313 patients were retrospectively reviewed. Recipients of *en-bloc* two kidney allografts (2 cases), or for whom hypothermic machine perfusion (HMP) pump data was not available (17 cases) were subsequently excluded, resulting in a final study population of 294 patients. The requirement for informed consent was waived by the institutional review board.

All recipients' demographic, comorbidities, preoperative medications, and echocardiographic data within one year prior to transplant, as well as laboratory evaluation upon admission and intraoperative data were recorded. Donor data and kidney donor profile index (KDPI) were extracted from the United Network for Organ Sharing DonorNet® database. All donor kidneys were biopsied at our transplant center and placed on hypothermic machine perfusion (HMP) pumps using a DCM-100 Cassette (RM3 Renal Preservation Machine, Waters Instruments, Rochester, MN), and perfused with Belzer-MPS Machine Perfusion Solution (Trans-Med Corporation, Elk River, MN) at 4 °C, as previously described[16]. A HMP pump resistance upper limit index of 0.3 mmHg/mL/min is used at our center and as such no allografts transplanted in this study had a terminal resistance value above this cutoff.

Study variables definition

Cold storage time: Time from donor cross-clamp until the allograft was placed on the HMP pump[17]. Total cold ischemia time: Time from donor cross-clamp until the allograft was taken out of ice and placed on the surgical field, inclusive of time spent on the HMP pump. Total warm ischemia time: Time from when the kidney was taken out of ice until reperfusion. HMP pump parameters are reported as terminal values at the time the kidney was removed from pump. Blood pressures measured at baseline (i.e before induction of general anesthesia), 5 min and 30 min post-reperfusion, and immediately upon arrival to either the post-anesthesia care unit (PACU) or the intensive care unit were extracted from the anesthesia record. Hypotension was defined as a decrease in mean arterial pressure (MAP) of ≥ 30 mmHg from baseline[18]. Diagnosis of postoperative pulmonary edema was based on radiographic evidence of pulmonary edema as determined by a board-certified radiologist coupled with clinical symptomatology requiring supplemental oxygen or mechanical ventilation. A postoperative adverse cardiac event was defined as the occurrence of myocardial infarction, new-onset atrial or ventricular arrhythmia, or cardiac arrest within the first postoperative month. Perioperative surgical complications were evaluated using the Clavien-Dindo classification grading system[19]. Occurrence of DGF, the primary study outcome, was defined as the need for dialysis within seven days after transplantation as determined by the attending transplant nephrologist[20,21]. Graft function was evaluated at one week and six months post-transplant using the estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration equation[22]. Graft failure was defined as either a permanent need for dialysis or death with a functioning graft and was evaluated from the time of transplant until one year after transplantation[16].

Intraoperative protocol

All patients underwent ABO-compatible DDKTs under general endotracheal anesthesia with radial arterial line for hemodynamic monitoring placed after induction of general anesthesia. Our local protocol targeted a MAP ≥ 100 mmHg starting at the time of reperfusion of allograft until arrival to the postoperative unit. This hemodynamic goal was primarily achieved with crystalloid and/or colloid, reserving ephedrine or phenylephrine bolus administration for severe or refractory hypotension (MAP ≤ 65 mmHg and/or decrease in MAP of ≥ 30 mmHg from baseline) at the discretion of the anesthesia provider. Dopamine infusion was always used whenever prolonged vasopressor support was indicated. As per local protocol, all recipients received intravenous (iv) furosemide 50 mg and mannitol 12.5 g 10 min prior to, as well as 10 min after reperfusion. In recipients of a high-risk allograft, as deemed by the transplant surgeon, a furosemide infusion of 20 mg/h was initiated shortly after the second 50mg bolus dose and continued in the postoperative unit. All patients received induction immunosuppression with three immunosuppressive agents each: iv basiliximab (20 mg, 2 doses), rabbit antithymocyte globulin (1 mg/kg daily, 3 doses), and methylprednisolone (500 mg, 3 doses)[23].

Intraoperative iv heparin was selectively administered to recipients deemed high risk for graft thrombosis by the transplant surgeon. Accordingly, seven patients received intraoperative IV bolus heparin with doses ranging between 1000-3000 units. Routine postoperative thromboprophylaxis consisted of heparin 5000 units subcutaneously twice daily. Surgical drains and ureteral stents were placed at surgeon discretion and not routinely utilized.

Statistical analysis

Categorical variables were expressed as percentages (%) and differences between the groups were assessed with chi-square or Fisher's exact test when appropriate. Continuous variables were expressed as median and interquartile ranges (25%-75%) and differences between the groups assessed with Wilcoxon rank-sum test. A bivariate analysis was performed to compare the groups with and without DGF regarding recipients', donors' and HMP pump variables, including recipient BMI, baseline MAP, donor terminal creatinine, cold ischemia time, cold storage time, and HMP pump flow rate and resistance. We subsequently determined the cut-off values for statistically significant continuous variables, using receiver operating characteristic analysis and Youden index[24]. A logistic regression model was then built for the cohort using a stepwise personality with a stopping rule P-value threshold of 0.10 for probability to enter or leave, conducted in a mixed direction, was performed to identify recipient, donor, HMP pump, and intraoperative predictors statistically associated with DGF. Clinically significant factors from Tables 1-3 were included as covariates to adjust for cofounders. Odds ratios (OR) and 95%CI were calculated. C-index was used to calculate the strength of the associations. The bootstrap method for 2500 iterations yielded bias-corrected C-index and 95%CI for the regression coefficients of the model[25]. Misclassification rates calculated the proportion of observations allocated to the incorrect group and represent the false-positive rate. Predictor's profiler and predictor's importance was explored for main and total effect. Main effect is the importance index that reflects the relative contribution of that factor alone and total effect is the importance index that reflects the relative contribution of that factor both alone and in combination with other factors[26]. Cochran-Armitage trend test was used to assess the association between a cut-off value of baseline MAP and intraoperative phenylephrine[27]. The statistical software used for all study calculations was JMP Pro 14.0 (SAS Institute Inc., Cary, NC, United States).

RESULTS

The incidence of the primary outcome DGF was 27% (79/294).

Preoperative

A descriptive analysis of preoperative clinical characteristics, stratified by DGF *vs* non-DGF, is shown in Table 1. Comorbidities associated with metabolic syndrome were more common in recipients with DGF when compared to non-DGF, including obesity with BMI ≥ 30 kg/m^2 [47% (37/79) *vs* 28% (60/215) respectively, OR 2.3, 95%CI: 1.335-3.878, χ^2 = 9.4, P = 0.002], diabetes [53% (42/79) *vs* 31% (66/215) respectively, OR 2.6, 95%CI: 1.510-4.347, χ^2 = 12.5, P = 0.001], dyslipidemia [72% (57/79) *vs* 47% (102/215) respectively, OR 2.9, 95%CI: 1.639-5.025, χ^2 = 14.2, P = 0.001], and coronary artery disease (CAD) [35% (28/79) *vs* 18% (39/215) respectively, OR 2.5, 95%CI: 1.391-4.411, χ^2 = 9.8, P = 0.002]. Dialysis-associated hypotension requiring oral vasopressor therapy with midodrine was recorded in 3% (8/294) of recipients with similar incidences in DGF and non-DGF groups [3% (2/79) *vs* 3% (6/215) respectively, OR 0.90, 95%CI: 0.178-4.578, χ^2 = 0.02, P = 0.90].

Intraoperative fluid and hemodynamic management

A descriptive analysis of intraoperative clinical characteristics, stratified by DGF *vs* non-DGF, is presented in Table 2. Administered crystalloids (type and volume), albumin, and blood products were similar in recipients with or without DGF. A clinically insignificant increase in estimated blood loss was observed in DGF recipients [150 *vs* 100 mL in non-DGF, χ^2 = 6.5; P = 0.01].

In a majority of recipients (70%, 206/294) the baseline MAP was ≥ 100 mmHg. Both baseline and first postoperative MAPs were slightly lower in the DGF group compared to non-DGF [107 mmHg *vs* 112 mmHg respectively, χ^2 = 3.1, P = 0.08 and 102 *vs* 105 respectively, χ^2 = 2.9, P = 0.09]. A cut-off baseline MAP < 110 mmHg was statistically associated with DGF (χ^2 = 4.6, P = 0.02; OR 1.8, 95%CI: 1.049-3.047]. MAPs at 5- and 30-min post-reperfusion were similar in DGF and non-DGF recipients. The targeted post-reperfusion MAP (≥ 100 mmHg) was achieved in only nearly 25% of recipients at 5 min (74/294) and 30 min (75/294) post reperfusion, and in 60% of patients (177/294) on arrival to the postoperative unit (Table 2), but similarly in recipients with or without DGF. Likewise, incidences of hypotension, with a decrease from baseline values in MAP ≥ 30 mmHg, at 5-min [24% (18/79) *vs* 26% (56/215) respectively, OR 0.83, 95%CI: 0.453-1.528, χ^2 = 0.35, P = 0.55] and on arrival to the postoperative unit

Table 1 Preoperative characteristics of recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Transplant, yr, *n* (%)				0.18
2016	175 (60)	52 (66)	123 (57)	
2017	119 (40)	27 (34)	92 (43)	
Age, yr	56 (44-64)	58 (50-63)	54 (41-64)	0.06
Male, *n* (%)	186 (63)	50 (63)	136 (63)	0.99
Race, *n* (%)				0.35
Caucasian	48 (16)	8 (10)	40 (19)	
Afro-American	153 (52)	45 (57)	108 (50)	
Hispanic	88 (30)	25 (32)	63 (29)	
Other	5 (2)	1 (1)	4 (2)	
BMI, kg/m^2	28 (24-32)	29 (26-35)	27 (24-30)	0.001[a]
BMI ≥ 30 kg/m^2	97 (33)	37 (47)	60 (28)	0.002[a]
Redo transplant, *n* (%)	26 (8)	4 (5)	22 (10)	0.17
Dialysis type, *n* (%)				0.26
Peritoneal	24 (8)	6 (8)	18 (8)	
Hemodialysis	263 (90)	73 (92)	190 (88)	
Pre-dialysis	7 (2)	0 (0)	7 (3)	
Duration of dialysis, mo	67.4 (29.1-88.7)	67.4 (52.5-92.9)	67.1 (46.6-87.2)	0.37
Preoperative baseline laboratory				
WBC, × 10^3/μL	6.6 (5.5-8.2)	6.8 (5.7-8.5)	6.6 (5.4-8.1)	0.22
Hgb, g/dL	11.1 (10.2-12.1)	11.1 (10.2-12.9)	11.2 (10.1-12.2)	0.66
Hct, %	34.5 (31.0-37.6)	34.7 (31.2-37.0)	34.5 (30.9-37.8)	0.97
K^+, mmol/L	4.7 (4.3-5.2)	4.9 (4.4-5.4)	4.7 (4.3-5.1)	0.05
$HCO3^-$, mmol/L	26 (23-29)	26 (23-28)	26 (23-29)	0.36
Na^+, mmol/L	140 (138-142)	140 (138-143)	140 (138-142)	0.25
Creatinine, mg/dL	8.9 (6.7-11.2)	9.11 (7.1-11.1)	8.9 (6.7-11.2)	0.88
Medical history, *n* (%)				
Hypertension	285 (97)	77 (97)	208 (97)	0.75
Diabetes	108 (37)	42 (53)	66 (31)	0.001[a]
Dyslipidemia	159 (54)	57 (72)	102 (47)	0.001[a]
CAD	67 (23)	28 (35)	39 (18)	0.002[a]
Smoking	79 (27)	19 (24)	60 (28)	0.51
Preoperative medications, *n* (%)				
ACEi/ARB	99 (34)	19 (24)	80 (37)	0.03[a]
CC-blocker	134 (46)	35 (44)	99 (46)	0.79
Beta-blocker	168 (57)	47 (59)	121 (56)	0.62
Diuretic	33 (11)	12 (15)	21 (10)	0.19
Statin	107 (36)	43 (54)	64 (30)	0.001[a]
Aspirin	94 (32)	35 (44)	59 (27)	0.006[a]
Clopidogrel[1]	22 (7)	11 (14)	11 (5)	0.01[a]

Midodrine	8 (3)	2 (3)	6 (3)	0.9
Echocardiography				
LV EF < 50%, *n* (%)	8 (3)	3 (4)	5 (2)	0.49
DD Grade 2 or 3, *n* (%)	44 (15)	14 (18)	30 (14)	0.42
LVH, *n* (%)	183 (62)	55 (70)	128 (60)	0.11
RVSP, mmHg	28 (23-34)	27 (22-34)	28 (23-33)	0.91

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %.

[a]*P* < 0.05 denotes statistical significance.

[1]11 patients on both aspirin and clopidogrel.

BMI: Body mass index; DGF: Delayed graft function; WBC: White blood cell count; Hgb: Hemoglobin; Hct: Hematocrit; K^+: Potassium; NaHCO3: Sodium bicarbonate; Na^+: Sodium; CAD: Coronary artery disease; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CC-blocker: Calcium channel blocker; LVEF: Left ventricular ejection fraction; DD: Diastolic dysfunction; LVH: Left ventricular hypertrophy; RVSP: Right ventricular systolic pressure.

[9% (7/79) *vs* 9% (20/215) respectively, OR 0.94, 95%CI: 0.383-2.324, χ^2 = 0.02, *P* = 0.90] were similar between DGF and non-DGF recipients. However, hypotension at 30 min post-reperfusion occurred more commonly in the non-DGF group 27% (57/215) *vs* 16% (13/79) in DGF group, but did not reach statistical significance (χ^2 = 3.2; *P* = 0.07).

Phenylephrine boluses were administered to 22% (64/294) of the cohort, and were statistically associated with DGF, insofar as 32% (25/79) of recipients with DGF received phenylephrine vs 18% (39/215) in recipients who did not develop DGF (OR 2.1, 95%CI: 1.161-3.759, χ^2 = 6.2; *P* = 0.01). An association between baseline MAP < 110 mmHg and intraoperative phenylephrine therapy was found in the Cochran-Armitage trend test (*Z* = 2.33, *P* = 0.02). Additionally, compared with untreated recipients, phenylephrine-treated recipients had lower MAPs at 5-min and 30-min post-reperfusion, and upon arrival to the PACU [103 *vs* 112 mmHg, χ^2 = 7.9, *P* = 0.005; 87 mmHg *vs* 91 mmHg, χ^2 = 4.1, *P* = 0.04; 87 mmHg *vs* 92 mmHg, χ^2 = 8.2, *P* = 0.01; and 97 mmHg *vs* 106 mmHg, χ^2 = 15.5; *P* < 0.001, respectively]. In 70 recipients (24%), the MAP 30 min post reperfusion was lower than baseline by more than 30 mmHg; 16 and 54 thereof were treated and not treated with phenylephrine, respectively. DGF occurred in 7 of the 16 (44%) and in 6 of the 54 (11%), respectively [OR 6.2, 95%CI: 1.691-22.882; χ^2 =8.7; *P* = 0.0032]. Of the 224 recipient without a similar decrease from baseline in MAP measured 30 min post reperfusion, 48 and 176 were treated and not treated with phenylephrine, respectively; DGF occurred in 18 of the 48 (38%) and 48 of the 176 (27%), respectively [OR 1.6, 95%CI: 0.810-3.109; χ^2 =1.8; *P* = 0.18].

Donor data

A descriptive analysis of donor and HMP pump data for recipients who did and did not develop DGF is presented in Table 3. Nearly half (46%) of kidney allografts used in our center were imports. A higher KDPI was recorded for imported *vs* local allografts [median 69% (42-86) *vs* 47% (23-68) respectively, χ^2 = 22, *P* = 0.001]. Cold ischemia and cold storage times were significantly longer in DGF *vs* non-DGF allografts, [30.6 h *vs* 26.4 h (χ^2 = 6.9; *P* =0.009); and 18.4 h *vs* 9.6 h (χ^2 = 9.9; *P* =0.002), respectively]. Similarly, HMP flows < 150 mL/min and resistance ≥ 0.23 mmHg/mL/min were recorded for allografts that developed DGF, see Table 3.

Postoperative and outcome data

A descriptive analysis of postoperative characteristics in DGF and non-DGF recipients is presented in Table 4. Based on the Clavien-Dindo classification, the overall surgical complication rate in the first month postoperatively was 19% (56/294), with a higher rate in recipients with DGF than in non-DGF recipients [32% (25/79) *vs* 14% (31/215) respectively, OR 2.7, 95%CI: 1.496-5.047; χ^2 = 11; *P* = 0.002]. Moreover, compared to non-DGF allografts, DGF was associated with significantly lower eGFR after six postoperative months, and higher incidence of 1-year graft failure [50.6 mL/min *vs* 73.3 mL/min (χ^2 = 31.8; *P* = 0.001), and 10% *vs* 1% (OR 8, 95%CI: 2.056-30.832, χ^2 = 12.2; *P* = 0.002), respectively]. The overall incidence of allograft failure at one year was 4% (11/294). Etiologies of graft failure were: (4) Rejection, (4) thrombosis within 1st post-transplant week, (1) chronic allograft nephropathy, and (2) deaths with a functioning graft (1 sepsis, and 1 cardiac event).

Table 2 Intraoperative characteristics for recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Surgery time, h	2.7 (2.0-3.9)	2.5 (1.8-4.4)	2.8 (2.2-3.9)	0.03[a]
Warm ischemia time, min	29 (24-36)	27 (23-34)	29 (24-36)	0.08
Fluid and electrolytes				
Crystalloid, L	2.0 (1.5-2.5)	2.0 (1.5-2.2)	2.0 (1.5-2.5)	0.97
Plasmalyte/Isolyte, *n* (%)	94 (32)	23 (29)	71 (33)	0.82
Normal saline, *n* (%)	161 (55)	45 (57)	116 (54)	
Combined, *n* (%)	39 (13)	11 (14)	28 (13)	
Weight based crystalloid (mL/kg)	24 (19-32)	22 (18-31)	25 (19-33)	0.11
Albumin, grams	25 (12.5-50)	25 (25-50)	25 (12.5-50)	0.66
Packed red blood cells, *n* (%)				0.46
None	224 (76)	60 (76)	164 (76)	
1 unit	39 (13)	11 (14)	28 (13)	
2 units	25 (9)	8 (10)	17 (8)	
3+ units	6 (2)	0 (0)	6 (3)	
Fresh frozen plasma, *n* (%)				0.38
None	287 (98)	79 (100)	208 (97)	
1 unit	2 (1)	0 (0)	2 (1)	
2+ units	5 (2)	0 (0)	5 (2)	
Platelets, *n* (%)				0.58
None	290 (99)	79 (100)	211 (98)	
1 unit	4 (1)	0 (0)	4 (2)	
Estimated blood loss, mL	100 (95-200)	150 (100-300)	100 (50-200)	0.01[a]
NaHCO3, mEq	50 (50-112.5)	50 (50-100)	50 (50-150)	0.76
$CaCl_2$, *n* (%)	210 71)	59 (75)	151 (70)	0.56
$CaCl_2$, g	1 (0.75-1.5)	1 (0.75-1.25)	1 (0.75-1.5)	0.65
Furosemide infusion, *n* (%)	192 (65)	44 (56)	148 (69)	0.04[a]
$NaHCO_3$, *n* (%)	54 (18)	11 (14)	43 (20)	0.31
Urine output, mL	75 (15-200)	28 (5-80)	100 (20-250)	< 0.0001[a]
Hemodynamics and inotropes				
MAP at baseline, mmHg	109 (96-122)	107 (95-118)	112 (96-123)	0.08
Baseline MAP < 110 mmHg, *n* (%)	159 (54)	51 (65)	108 (50)	0.02[a]
MAP 5 min post-reperfusion, mmHg	90 (81-100)	91 (79-97)	90 (82-100)	0.45
5 min post-reperfusion MAP < 100 mmHg, *n* (%)	220 (75)	61 (77)	159 (74)	0.61
Drop in MAP ≥ 30 mmHg from baseline -5 min post-reperfusion, *n* (%)	74 (25)	18 (24)	56 (26)	0.55
MAP 30 min post-reperfusion, mmHg	91 (82-100)	92 (82-101)	91 (83-99)	0.85
30 min post-reperfusion MAP < 100 mmHg, *n* (%)	218 (74)	54 (68)	164 (77)	0.15
Drop in MAP ≥ 30 mmHg from baseline -30 min post-reperfusion, *n* (%)	70 (24)	13 (16)	57 (27)	0.07
MAP 1st post-operative, mmHg	104 (95-113)	102 (92-110)	105 (96-113)	0.09
1st post-operative MAP < 100 mmHg, *n* (%)	117 (40)	35 (44)	82 (38)	0.34
Drop in MAP ≥ 30 mmHg from baseline -1st post-operative, *n* (%)	27 (9)	7 (9)	20 (9)	0.9

Dopamine, *n* (%)	5 (2)	2 (3)	3 (1)	0.61
Ephedrine, *n* (%)	74 (25)	25 (32)	49 (23)	0.12
Ephedrine dose, mg	10 (5-20)	10 (5-20)	10 (5-18)	0.62
Phenylephrine, *n* (%)	64 (22)	25 (32)	39 (18)	0.01[a]
Phenylephrine dose, mcg	200 (100-400)	200 (125-400)	200 (100-400)	0.64
Phenylephrine timing:				
None, *n* (%)	230 (78)	54 (68)	176 (82)	0.06
Before reperfusion, *n* (%)	39 (14)	14 (18)	25 (12)	
After reperfusion, *n* (%)	10 (3)	4 (5)	6 (3)	
Both before and after, *n* (%)	15 (5)	7 (9)	8 (4)	
Phenylephrine and Ephedrine, *n* (%)	37 (13)	16 (20)	21 (10)	0.02[a]

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %.
[a]*P* < 0.05 denotes statistical significance.
DGF: Delayed graft function; MAP: Mean arterial blood pressure; NaHCO3: Sodium bicarbonate; $CaCl_2$: Calcium chloride; OR: Operating room.

Employing logistic regression, eight risk factors for DGF were identified (see Table 5): Recipient BMI ≥ 30 kg/m^2; Baseline MAP < 110 mmHg, intraoperative phenylephrine administration; Cold storage time ≥ 16 h; Donation after cardiac death, donor history of CAD, donor terminal creatinine ≥ 1.9 mg/dL, and HMP pump resistance ≥ 0.23 mmHg/mL/min. Supplementary Table 1 delineates the eight predictors in order of importance. The whole model was statistically significant in its entirety ($\chi^2 = 87$, $P = 0.001$), and a C-index of 0.83 was calculated for these risk factors with a bias-corrected C-index of 0.84 (95%CI: 0.76-0.88). The model's calculated misclassification rate of 19% reflects its ability to accurately predict DGF in 81 of 100 recipients.

DISCUSSION

Higher-risk donor allografts provide a way to increase the deceased-donor kidney transplant pool, but have been associated with DGF. In our cohort, the incidence of DGF was 27%, which is consistent with the previously reported incidence[13,28-30]. Optimization of modifiable perioperative risk factors for the development of DGF would allow for improved transplantation outcomes, particularly improved early graft function, without shrinking the donor pool. The important role of intraoperative renal blood flow on early postoperative renal function has been known since the 1970's[31,32], and intraoperative hemodynamic variables are the focus of several recent outcome studies[12-15].

A novel finding of this study is the identification of pre-induction MAP < 110 mmHg as an independent risk factor for the development of DGF. This observation underscores the need of the newly grafted kidney for optimal perfusion pressure that is higher than the traditional normal[33]. A complex interaction between donor's and recipient's comorbidities, pre-procurement ischemia, procurement and organ storage conditions, along with peri-transplant factors result in such a unique perfusion requirement of the allograft[10]. Suboptimal blood pressure has previously been explored as a potential risk factor in the development of DGF. Thomas *et al*[13] reported that half of the patients in their study with a post-reperfusion systolic BP of less than 120 mmHg experienced DGF. More recent data showed that patients with a MAP of < 80 mmHg at the time of reperfusion were 2.4 times more likely to develop DGF[12].

The optimal intraoperative hemodynamic management of recipients of renal allografts remains controversial. Since several studies reported a reduced incidence of DGF with fluid loading[14,34,35], in this study we carefully evaluated outcomes in relation to crystalloid volume, weight-based crystalloid administration, crystalloid type, colloid volume, and colloid type. Our finding of a lack of an association between fluids administered and DGF is in accord with others[12,36,37], and a recent multicenter study[38].

Vasopressors may be indicated when volume loading is insufficient to obtain optimal allograft perfusion. Reported outcomes of perioperative vasopressor use in

Table 3 Donor and hypothermic machine perfusion pump characteristics for recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Donor characteristics				
Donor kidney				0.35
Left, *n* (%)	136 (46%)	33 (42%)	103 (48%)	
Right, *n* (%)	158 (54%)	46 (58%)	112 (52%)	
Donor location				0.001[a]
Local, *n* (%)	158 (54%)	27 (34%)	131 (61%)	
Import, *n* (%)	136 (46%)	52(66%)	84 (39%)	
Kidney donor profile index, %	53 (33-81)	61 (40-85)	49 (28-75)	0.006[a]
Donor age, yr	44 (32-56)	49 (36-56)	42 (30-55)	0.04[a]
Donor body mass index, kg/m^2	27 (23-31)	28 (25-33)	26 (23-31)	0.009[a]
Donation after cardiac death, *n* (%)	50 (17%)	23 (29%)	27 (13%)	0.001[a]
Donor cause of death				0.6
Anoxia, *n* (%)	119 (40%)	31 (39%)	88 (41%)	
Head trauma, *n* (%)	76 (26%)	18 (23%)	58 (27%)	
Stroke, *n* (%)	99 (34%)	30 (38%)	69 (32%)	
Donor cardiac arrest, *n* (%)	141 (48%)	40 (51%)	101 (47%)	0.58
Donor medical history				
Hypertension, *n* (%)	104 (35%)	32 (41%)	72 (33%)	0.28
Diabetes, *n* (%)	34 (12%)	12 (15%)	22 (10%)	0.24
Coronary artery disease, *n* (%)	27 (9%)	16 (20%)	11 (5%)	0.001[a]
Smoking, *n* (%)	70 (24%)	20 (25%)	50 (23%)	0.73
Heavy alcohol use, *n* (%)	65 (22%)	13 (16%)	52 (24%)	0.15
Admit creatinine, mg/dL	1.1 (0.9-1.4)	1.1 (0.9-1.5)	1.1 (0.9-1.30)	0.2
Terminal creatinine, mg/dL	1.0 (0.7-1.6)	1.3 (0.81-2.8)	0.9 (0.7-1.4)	0.001[a]
Terminal creatinine ≥ 1.9 mg/dL	63 (21%)	31 (39%)	32 (15%)	0.001[a]
Donor Biopsy: % glomerulosclerosis	3.9 (0-8.3)	4.6 (1.7-10)	3.4 (0-7.6)	0.14
HMP pump characteristics				
Cold ischemia time	28.5 (21.5-34.5)	30.6 (25.8-36.4)	26.4 (21.2-33.8)	0.009[a]
Cold ischemia time ≥ 26 h	172 (59%)	58 (73%)	114 (53%)	0.002[a]
Cold storage time, h	10.6 (6.8-20.6)	18.4 (7.1-24.7)	9.6 (6.8-18.9)	0.002[a]
Cold storage duration ≥ 16 h	120 (41%)	46 (58%)	74 (34%)	0.001[a]
Total pump time, h	13.3 (8.4-19.2)	13.1 (8.2-18.9)	13.4 (8.4-19.7)	0.37
Final pump parameters				
Flow, mL/min	141 (123-156)	127 (117-148)	142 (126-159)	0.001[a]
Resistance, mmHg/mL/min	0.20 (0.15-0.25)	0.24 (0.16-0.29)	0.19 (0.15-0.24)	0.001[a]
Systolic pressure, mmHg	34 (29-40)	35 (30-40)	33 (27-39)	0.009[a]
Diastolic pressure, mmHg	24 (18-29)	26 (19-30)	23 (18-29)	0.09
Pump flow < 150 mL/min	190 (65%)	65 (82%)	125 (58%)	0.001[a]
Pump resistance ≥ 0.23 mmHg/mL/min	115 (39%)	47 (59%)	68 (32%)	0.001[a]

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages (%).
[a]*P* < 0.05 denotes significance.
DGF: Delayed graft function; HMP: Hypothermic machine perfusion.

Table 4 Postoperative characteristics for recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Post-operative location, *n* (%)				0.95
PACU	230 (78)	62 (78)	168 (78)	
ICU	64 (22)	17 (22)	47 (22)	
Extubation in OR	282 (96)	74 (94)	208 (97)	0.24
Reintubation, *n* (%)				
Within 48 h	4 (1)	3 (4)	1 (0.5)	0.06
Within 1 wk	6 (2)	4 (5)	2 (1)	0.05
Pulmonary edema, *n* (%)				
Within 48 h	11 (4)	5 (6)	6 (3)	0.16
Within 1 wk	13 (4)	6 (8)	7 (3)	0.11
Adverse cardiac events, *n* (%)				
Within 48 h	10 (3)	2 (3)	8 (4)	0.62
Within 1 wk	15 (5)	3 (4)	12 (6)	0.54
Within 1 mo	17 (6)	4 (5)	13 (6)	0.1
Clavien-Dindo at 1 mo, *n* (%)[1]				
None	238 (81)	54 (68)	184 (86)	0.002[a]
Grade I	4 (1)	0 (0)	4 (2)	
Grade II	14 (5)	6 (8)	8 (4)	
Grade IIIa	19 (6)	11 (14)	8 (4)	
Grade IIIb	13 (4)	4 (5)	9 (4)	
Grade IVa	4 (1)	3 (4)	1 (0.5)	
Grade IVb	1 (1)	1 (1)	0 (0)	
Grade V	1 (1)	0 (0)	1 (0.5)	
Total complications	56 (19)	25 (32)	31 (14)	
Length of stay, d	6 (5-8)	8 (6-12)	6 (5-7)	0.001[a]
eGFR, 6 mo, mL/min	65.3 (48.4-81.6)	50.6 (36.2-71.0)	73.3 (58.6-89.5)	0.001[a]
eGFR < 60 mL/min at 6 mo, *n* (%)	120 (41)	51 (65)	69 (32)	0.001[a]
Graft survival at 1 yr, *n* (%)[2]	283 (96%)	71 (90)	212 (99)	0.002[a]
Patient survival at 1 yr, *n* (%)	292 (99)	79 (100)	213 (99)	0.34

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %.
[a]*P* < 0.05 denotes significance.
[1]Includes ultrasound evidence of 19 perinephric fluid collections not requiring intervention, and 32 perinephric fluid collections with intervention.
[2]4 graft failure attributed to thrombosis were due to technical difficulty: two allografts had single renal arteries and two allografts had two renal arteries, only one of which underwent arterial reconstruction in which the inferior portal artery was connected to the vein in a side-to-side anastomosis.
PACU: Post-anesthesia care unit; ICU: Intensive care unit; BP: Blood pressure; eGFR: Estimated glomerular filtration rate.

kidney transplant are incongruous. Day *et al*[39] suggested that postoperative phenylephrine administration was associated with the development of DGF, but was not implicated in allograft function by the time of hospital discharge. A recent multicenter study identified intraoperative ephedrine use, but not phenylephrine, as an independent predictor for the development of DGF[38]. These studies, however, did not assess whether the association between vasopressor use and DGF is due to an undesirable effect of the vasopressor on the outcome, or if vasopressor use solely serves as a surrogate of suboptimal perfusion and/or volume status. In the current study, we identified the use of phenylephrine intraoperatively, but not ephedrine, as an independent risk factor for the development of DGF. Further, we performed subgroup analyses to evaluate the hemodynamic and fluid resuscitation of phenylephrine-treated and untreated recipients (Supplementary Table 2). There were no statistically significant differences in terms of volume of crystalloid administered between recipients treated and not treated with phenylephrine. Phenylephrine, however, appears to be associated with an increase in DGF in all recipients, particularly in recipients whose MAP 30 min post-reperfusion was lower than baseline by more than 30 mmHg (OR of 6.2 and 1.6, with and without similar post reperfusion hypotension, respectively). Even so, it's unlikely that phenylephrine-induced vasoconstriction is the culprit[40], since the effect of a bolus dose is brief and the phenylephrine was administered before reperfusion in more than half of the recipients (Supplementary Table 2). Plausibly, intraoperative phenylephrine use is a surrogate of an unmeasured hemodynamic variable, *e.g.* postoperative allograft perfusion[12,13], or another clinical parameter that influences the outcome.

This study's non-modifiable predictors of DGF (Table 5) are consistent with previously reported risk factors[7,8,17,41-46]. Of note, we found over a 5-fold increase in incidence of DGF in allografts recovered from donors with a history of CAD. This study finding of poorer transplantation outcomes in recipients with DGF, such as postoperative reintubation, increased length of stay, and reduced graft function at 6 mo (Table 4), is in agreement with previous reports[9,47]. The association of DGF with reduced graft and recipient survival is contentious; as such, our findings of an association with reduced 1-year graft survival, but not with 1-year recipient survival (Table 4) are in accord with some but not all previous studies[9,47].

The limitations of this study include: (1) Its retrospective single transplant center nature and as such the results may not be readily extrapolated to other centers with diverse practices; (2) The timing of the most recent pre-transplant dialysis was not available; (3) The hemodynamic picture of the entire perioperative period was not captured; most importantly, the postoperative period was not assessed beyond the first set of vitals upon arrival to the post-anesthesia unit; (4) The study sample size was relatively small therefore limiting the possibility of separate analysis of outcome variables other than DGF, such as graft failure, which only occurred in 3.7% (11/294) of the population; and (5) Variations in individual patient adherence to immunosuppression regimens was not captured but may have contributed to graft outcomes.

CONCLUSION

In conclusion, this study identifies a baseline mean arterial pressure less than 110 mmHg and intraoperative phenylephrine therapy as predictive of DGF along with reaffirming other previously well-established risk factors. Further studies are needed to explore means to improve outcomes of recipients with suboptimal baseline or intraoperative blood pressure.

Table 5 Perioperative predictors associated with delayed graft function

	OR	95%CI	*P* value
Preoperative recipient risk factor			
Recipient BMI ≥ 30 kg/m^2	3.8	1.947-7.548	0.0001[a]
Intraoperative recipient risk factor			
Baseline MAP < 110 mmHg	2.2	1.098-4.326	0.0260[a]
Phenylephrine usage	2.2	1.040-4.820	0.0392[a]
Donor risk factors			
Cold storage time ≥ 16 h	2.8	1.378-5.666	0.0044[a]
Donation after cardiac death	4.4	1.872-10.225	0.0007[a]
Donor with history of CAD	5.8	2.133-16.033	0.0006[a]
Terminal creatinine ≥ 1.9 mg/dL	4.3	2.041-8.855	0.0001[a]
HMP pump risk factor			
Resistance ≥ 0.23 mmHg/mL/min	2.2	1.132-4.307	0.0201[a]

[a]*P* < 0.05 denotes significance.

OR: Odds ratio; BMI: Body mass index; MAP: Mean arterial pressure; CAD: Coronary artery disease; HMP: Hypothermic machine perfusion pump.

ARTICLE HIGHLIGHTS

Research background

There is a profound need to increase the availability of deceased donor kidney transplantation (DDKT) to address the high incidence of kidney failure. However, challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount.

Research motivation

Higher-risk kidney allografts more frequently exhibit delayed graft function (DGF), which has previously been associated with adverse outcomes such as acute rejection, chronic allograft nephropathy, shorter allograft survival, and increased costs. Furthermore, prior studies have pointed to an association between recipients' blood pressure and the occurrence of DGF but have conflicted on the clinical setting and unique patient characteristics that may predispose to it.

Research objectives

A clear need exists for the identification and optimization of modifiable perioperative risk factors associated with DGF. We aim to identify risk factors associated with DGF, with a particular focus on perioperative hemodynamic factors, since these can be more readily optimized to improve graft and patient outcomes.

Research methods

Consecutive adults undergoing DDKT between January 2016 and July 2017 were identified with a study population of 294 patients. All donor data and recipients' demographic, comorbidities, preoperative medications, and echocardiographic data within one year prior to transplant, as well as laboratory evaluation upon admission and intraoperative data were recorded. The primary outcome was the occurrence of DGF.

Research results

The incidence of DGF was 27%. Under logistic regression, eight independent risk factors for DGF were identified including recipient body mass index ≥ 30 kg/m^2, baseline mean arterial pressure < 110 mmHg, intraoperative phenylephrine administration, cold storage time ≥ 16 h, donation after cardiac death, donor history of coronary artery disease, donor terminal creatinine ≥ 1.9 mg/dL, and a hypothermic machine perfusion (HMP) pump resistance ≥ 0.23 mmHg/mL/min.

Research conclusions

We delineate the association between DGF and recipient characteristics of pre-induction MAP below 110 mmHg, metabolic syndrome, donor-specific risk factors, HMP pump parameters, and intraoperative use of phenylephrine.

Research perspectives

Future studies with larger multicenter cohorts are needed to further explore means to improve outcomes of recipients with suboptimal baseline or intraoperative blood pressure.

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ORIGINAL ARTICLE

Observational Study

Donor defects after lymph vessel transplantation and free vascularized lymph node transfer: A comparison and evaluation of complications

Gunther Felmerer, Dominik Behringer, Nadine Emmerich, Marian Grade, Adam Stepniewski

ORCID number: Gunther Felmerer 0000-0002-0935-1208; Dominik Behringer 0000-0003-2192-5152; Nadine Emmerich 0000-0003-2659-2422; Marian Grade 0000-0001-9527-5362; Adam Stepniewski 0000-0002-2608-5925.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Gunther Felmerer, Dominik Behringer, Adam Stepniewski, Division of Plastic Surgery, Department for Trauma Surgery, Orthopedics and Plastic Surgery, University Medical Center Goettingen, Goettingen 37075, Lower Saxony, Germany

Nadine Emmerich, Georg-August University Goettingen, University Medical Center Goettingen, Goettingen 37075, Lower Saxony, Germany

Marian Grade, Department of General, Visceral and Pediatric Surgery, University Medical Center Goettingen, Goettingen 37075, Lower Saxony, Germany

Corresponding author: Adam Stepniewski, MD, Doctor, Surgeon, Division of Plastic Surgery, Department for Trauma Surgery, Orthopedics and Plastic Surgery, University Medical Center Goettingen, Robert-Koch-Strasse 40, Goettingen 37075, Lower Saxony, Germany.
adam.stepniewski@med.uni-goettingen.de

Abstract

BACKGROUND

Secondary lymphedema after surgical interventions is a progressive, chronic disease that is still not completely curable. Over the past years, a multitude of surgical therapy options have been described.

AIM

To summarize the single-center complications in lymph vessel (LVTx) and free vascularized lymph node transfer (VLNT).

METHODS

In total, the patient collective consisted of 87 patients who were undergoing treatment for secondary leg lymphedema during the study period from March 2010 to April 2020. The data collection was performed preoperatively during consultations, as well as three weeks, six months and twelve months after surgical treatment. In the event of complications, more detailed follow-up checks were carried out. In total n = 18 robot-assisted omental lymph node transplantations, n = 33 supraclavicular lymph node transplantations and n = 36 Lymph vessel transplantations were analyzed. An exemplary drawing is shown in Figure 1. A graphical representation of patient selection is shown in Figure 2. Robotic harvest was performed with the Da Vinci Xi Robot Systems (Intuitive Surgical, CA,

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RESULTS

In total, 11 male and 76 female patients were operated on. The mean age of the patients at study entry was: omental VLNT: 57.45 ± 8.02 years; supraclavicular VLNT: 49.76 ± 4.16 years and LVTx: 49.75 ± 4.95 years. The average observation time postoperative was: omental VLNT: 18 ± 3.48 mo; supraclavicular VLNT: 14.15 ± 4.9 and LVTx: 14.84 ± 4.46 mo. In our omental VLNT, three patients showed a slight abdominal sensation of tension within the first 12 postoperative days. No other donor side morbidities occurred. No intraoperative conversion to open technique was needed. Our supraclavicular VLNT collective showed 10 lift defect morbidities with one necessary surgical intervention. In our LVTx collective, 12 cases of donor side morbidity were registered. In one case, surgical intervention was necessary.

CONCLUSION

Concerning donor side morbidity, robot-assisted omental VLNT is clearly superior to supraclavicular lymph node transplantation and LVTx.

Key Words: Lymph surgery; Vascularized lymph node transfer; Lymph vessel transfer; Robot-assisted surgery; Da Vinci Xi; Donor side morbidity

Core Tip: Secondary lymphedema after surgical interventions is a progressive, chronic disease that is still not completely curable. Since the establishment of laparoscopic minimally invasive surgery in everyday clinical practice and, most recently, further development using robot-assisted procedures, there have been significant changes in reconstructive lymph surgery. In our study we wanted to summarize our single-center complications in lymph vessel and free vascularized lymph node transfer. The patient collective consisted of 87 patients. In summary, robot-assisted omental vascularized lymph node transfer is clearly superior to supraclavicular vascularized lymph node transfer and lymph vessel due to the reliably low donor side morbidity.

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INTRODUCTION

Secondary lymphedema after surgery is a progressive, chronic disease that is still not completely curable. In the literature, a multitude of surgical therapy options have been described over the past years[1-5].

In this thesis, we will discuss a study being undertaken since November 2017 in our clinic according to the established method of robot-assisted lymph node transplantation from the omentum[6].

The autologous supraclavicular lymph node transplantation[7] and the lymph vessel transplantation according to Baumeister[8] will be used as comparative material.

The latter two therapy options have been used internationally since the establishment of microsurgery and for a long time in the main field of plastic surgery at the University Medical Center in Goettingen and have already shown promising results[9-11]. The former surgical method, in the form it has been performed in our clinic, represents a novelty and combines the advantages of a minimally invasive intervention using the Da Vinci surgical robot with the already known advantages of lymph node transplantation. Exemplary drawing of the individual donor sides is shown in Figure 1.

Since this is a procedure which requires the opening of the abdominal cavity, any

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abdominal complications should be worked out in this study. These should be compared with the lifting defect morbidity of the other two procedures. The data collection of the omental patient population was carried out preoperatively at the time of presentation in the consulting room, perioperatively as well as three weeks, six months and twelve months after surgery.

The aim of this study is to examine the complications of robot-assisted lymph node transfer in the treatment of secondary limb lymphedema in comparison to already known procedures in our clinic.

MATERIALS AND METHODS

In this study, data from three different collectives were collected and evaluated. A total of 87 patients undergoing treatment at our clinic between March 2010 and April 2020 were included. The evaluation included data was collected at each appearance during consultation hours, during surgical treatment and during stationary care.

Inclusion criteria for all collectives were, in the case of tumor suffering, a permanent remission and the absence of infections and inflammations. In addition, an adequate conservative therapy over a period of at least half a year should have been carried out beforehand. Some patients were advised to undergo inpatient rehabilitation with Complex Physical Decongestion before surgery.

The procedure for selecting the surgical procedure is shown in Figure 2.

Omental lymph node transplantation robot-assisted

A total of 18 patients could be included in the study section (one man, 17 women). The mean age of the patients at study entry was 57.45 ± 8.02 years (range: 40-75 years), the mean observation period was 18 ± 3.48 mo (range: 12-27 mo).

The main focus of the anamnestic interview was on the causes, the triggers, the latency period, the already performed conservative therapy and the question of erysipelas or other complications. Postoperatively, the anamnestic questioning of gastrointestinal symptoms was essential. Necessary inclusion criterion for the intervention was the removal of the corresponding lymph nodes in the inguinal or axillary region during the initial intervention. Patients with removed pelvic, paraaortic and only sentinel lymph node removal were not included. Lymph vessel transplantation or lymphovenous anastomosis were offered to these patients if surgery was desired and indication was given.

Postoperatively, the patients were called in for consultation at regular intervals to monitor their progress.

An essential prerequisite for performing an autologous lymph node transplant at our clinic is the removal of the inguinal or axillary lymph nodes. Here it is important that the removal of a single lymph node, for example a sentinel lymph node, or a lymph node biopsy does not provide sufficient indication. A transplantation into a non-functional region, such as an elbow or ankle, is not performed at our clinic. Consequently, only transplantations into the axilla or groin are performed.

The robot-assisted abdominal part of the operation is carried out in cooperation with colleagues from the general and visceral surgery department of the hospital. The da Vinci Xi robot system (Intuitive Surgical, CA, United States) is used for omental flap harvest.

Cervical lymph node transplantation

A total of 33 patients could be included in this study section (two men, 31 women). The mean age of the patients at study entry was 49.76 ± 4.16 years (range: 22-77 years), the mean observation period was 14.15 ± 4.9 mo (range: 4-66 mo).

The main focus of the anamnestic interview was on the causes, the triggers, the latency period, the conservative therapy already carried out and the question of erysipelas and other pre- and postoperative complications. As already described, necessary inclusion criterion for the intervention was the removal of the corresponding lymph nodes in the inguinal or axillary region during the initial intervention. Postoperatively, the patients were called in for consultation with the plastic surgery department at regular intervals to monitor their progress.

Lymph vessel transplantation

A total of 36 patients could be included in this study section (eight men, 28 women). The mean age of the patients at study entry was 49.75 ± 4.95 years (range: 15.9-60.7 years), the mean observation period was 14.84 ± 4.46 mo (range: 4-57 mo).

Figure 1 Exemplary drawing of the individual donor sides.

The main focus of the anamnestic interview was, as in the other groups, the causes, the triggers, the latency period and the conservative therapy already carried out and the question of erysipelas or other complications. Necessary inclusion criteria for the procedure was a lack of swelling in the area of the donor region. If the patients reported a corresponding swelling tendency after primary surgery, no lymph vessel transplantation was performed, even if there was no lymphedema in the area of the donor leg when the patient was seen during consultation. If, on the day of the operation, after intraoperative injection of patent blue, a dermal backflow was observed in the area of the donor leg, no lymph vessel transplantation was performed either. In such cases, lymphovenous anastomoses were applied. The patients were informed about this procedure preoperatively. In our lymph vessel group from 2010 to 2018, this occurred once.

Postoperatively, patients were seen during consultation hours of the plastic surgery department at regular intervals for follow-up.

RESULTS

Omental lymph node transplantation robot-assisted

A total of n = 18 patients could be included in the robot-assisted vascularized lymph node transfer (VLNT) study (one man, 17 women). The mean age of the patients at study entry was 57.45 ± 8.02 years (range: 40-75 years), the mean observation period was 18 ± 3.48 mo (range: 12-27 mo). In eight cases the right, in ten cases the left extremity was affected. According to the International Society of Lymphology (ISL) classification, 15 patients were classified as stage II, three patients as stage III. A total of eight leg lymphedema and ten arm lymphedema were operated on. Breast cancer was the most frequent primary diagnosis with n = 10 patients. The second most frequent cause was cervical carcinoma and vulva carcinoma with a frequency of n = 2 each. With a frequency of n = 1 each, surgical treatment was performed for a liposarcoma of the thigh, squamous cell carcinoma of the penis, malignant melanoma

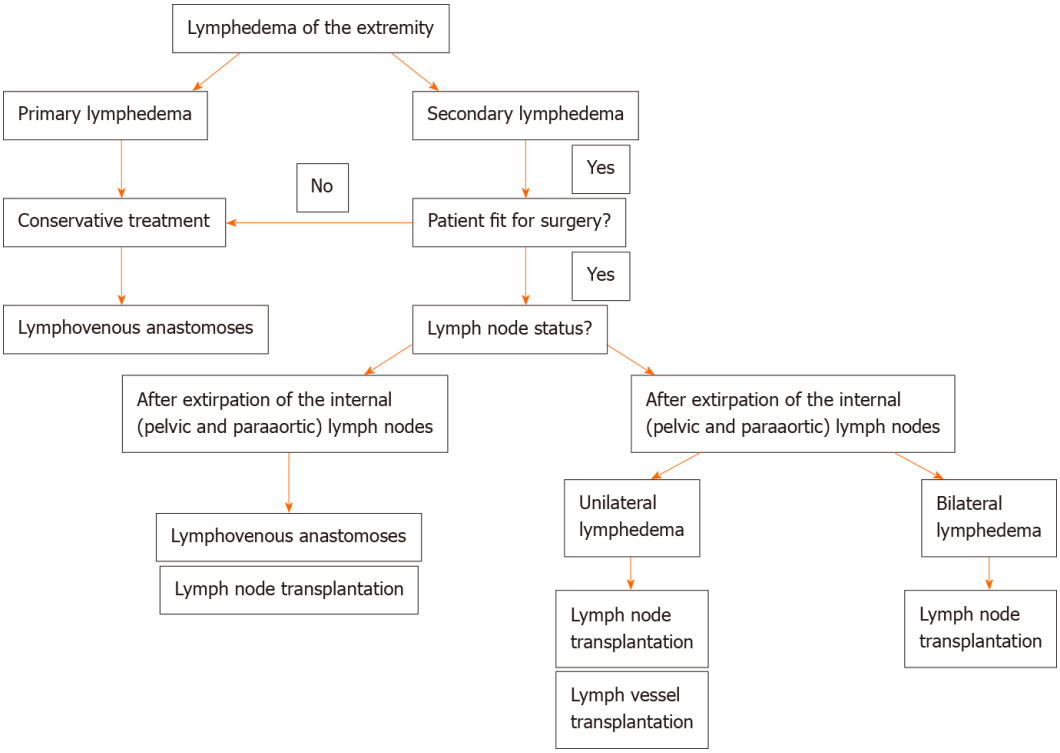

Figure 2 Flowchart showing the selection of the surgical procedure.

and a malignant peripheral neuroectodermal tumor. Six patients had received radiochemotherapy after primary surgery. Three patients received pure radiotherapy. Two patients received chemotherapy. All patients underwent lymphonodectomy in primary surgery. The average time from diagnosis to surgery was 91.64 ± 48.98 mo (range: 6-204 mo). Three of the surgical patients reported recurrent erysipelas of the corresponding lymphedematous extremity preoperatively. Two of them had three episodes per year and one patient had an average of four episodes. None of these patients suffered from recurrent erysipelas of the corresponding limb during the postoperative observation period. Three patients reported a slight tension in the abdominal area in the early postoperative phase with rapidly decreasing symptoms in the first 12 d (Table 1). A total of 5/18 patients had already undergone abdominal surgery. Among the procedures performed were two laparoscopic hysterectomies, one laparoscopic ovariectomy, one exploratory laparoscopy, one laparoscopic cholecystectomy and one robot-assisted pelvic lymphonodectomy. None of the surgical patients required an intraoperative change to an open procedure with medial laparotomy.

Cervical lymph node transplantation

A total of 33 patients could be included in the cervical lymph node group (two men, 31 women). The mean age of the patients at study entry was 49.76 ± 4.16 years (range: 22-77 years), the mean observation period was 14.15 ± 4.9 mo (range: 4-66 mo). In 17 cases the left, in 16 cases the right extremity was affected. According to the ISL classification, two patients were classified as stage III, the remaining 31 as stage II. In total, 13 Leg and 20 arm lymphedema were performed. Breast cancer was the most frequent primary diagnosis in the cervical lymph node group with n = 20 patients. The second most frequent cause was vulvar carcinoma and malignant melanoma with n = 3 cases each. n = 2 patients each underwent primary surgery for cervical carcinoma and liposarcoma. With n = 1 each, a lipoma of the thigh, endometrial carcinoma and lymphedema after inguinal hernia and removal of the inguinal lymph nodes were performed.

Seventeen patients had received radiochemotherapy after primary surgery. Three patients received pure radiotherapy. Two patients received pure chemotherapy. The average time from diagnosis to surgery was 72.87 ± 17.36 mo (range: 6-216 mo). Three patients reported recurrent erysipelas preoperatively. In two of the three patients, no recurrent erysipelas occurred in the follow-up period of one year.

Table 1 Donor side morbidity after robot-assisted omental vascularized lymph node transfer

Complications overview robot-assisted omental lymph node transfer			
Donor side	Type	Quantity	Therapy
	Abdominal pain	3	Declining spontaneously

Only supraclavicular lymph nodes were used as donor nodes in our clinic. A total of 24 right and nine left cervical lymph node packages were removed and used for transplantation.

A total of 10 complications occurred in 33 surgical patients during the inpatient and post-operative treatment. A tabular list of the individual complications as well as their number and therapy is given in Table 2.

In terms of donor side morbidities, three seromas worthy of puncture occurred poststationarily. On one occasion, a wound infection was found, which decreased well under antibiotic therapy. One lymphocele was found, which was punctured in an outpatient treatment. A persistent lymph fistula in the left cervical region had to be surgically revised and closed. In the case of significant cervical soft tissue swelling, one patient developed a temporary Horner's syndrome, which, however, regressed in the inpatient course. In the first follow-up, three weeks after surgery, no symptoms remained. One patient complained postoperatively about a hypertrophic, painful scar in the neck region. With two triamine infiltrations, a significant improvement of the symptoms could be achieved. Another patient complained postoperatively of hyposensitivity in the clavicular region.

Lymph vessel transplantation

A total of 36 patients could be included in the study (eight men, 28 women). The mean age of the patients at study entry was 49.75 ± 4.95 years (range: 15.9-60.7 years), the mean observation period was 14.84 ± 4.46 mo (range: 4-57 mo). In 18 cases, the left extremity was affected, in 15 cases the right extremity. Three patients were affected on both sides. According to the ISL classification five patients were classified as stage III, the remaining 31 as stage II. A total of 22 Legs, 11 arms, two lymphedema in the facial area and one lymphedema in the genital area were operated on. Cervical carcinoma was the most frequent primary diagnosis in the lymph vessel group with n = 13 patients. The second most frequent cause was breast carcinoma with n = 11 cases followed by malignant melanoma with n = 2 affected patients. This was followed by endometrial carcinoma, ovarian carcinoma, squamous cell carcinoma of the lower mouth, prostate carcinoma, leiomyosarcinoma, seminoma, renal cell carcinoma, non-Hodgkin's lymphoma, postinfectious lymphedema and lymphedema after massive acne vulgaris with n = 1 each.

Nineteen patients had received radiochemotherapy after primary surgery. Three patients received pure radiotherapy. One patient received chemotherapy.

The average time from diagnosis to surgery was 51.45 ± 13.05 mo (range: 12-137 mo).

Two patients reported recurrent erysipelas preoperatively. In one of the two patients, no recurrent erysipelas occurred in the follow-up period of one year.

As total of 5 different donor side morbidities occurred. One lymphocele occurred, which closed after five punctures. Two wound dehiscences with wound healing disturbances were seen. Two wound infections occurred, which were treated conservatively with antibiotics. Two lymph fistulas occurred, which stopped spontaneously after increasing albumin levels. In five of the 36 patients, there was an increase in the circumference of the donor leg. All five patients were fitted with appropriate compression stockings. One patient was equipped with compression stockings on the foot with a circular knit. Three patients required knee stockings with a circular knit. The last patient required a complete thigh stocking of compression class I with a flat knit (Table 3).

DISCUSSION

Since the establishment of laparoscopic minimally invasive surgery in everyday clinical practice and, most recently, further development using robot-assisted procedures, there have been significant changes in reconstructive lymph surgery. The robot-assisted lymph node transfer from the omentum was first described in 2016[12].

Table 2 Donor side morbidity after cervical vascularized lymph node transfer

Complications overview cervical lymph node transfer			
Donor side	**Type**	**Quantity**	**Therapy**
	Horner syndrome (stationary)	1	Declining spontaneously
	Supraclavicular/cervical hypaesthesia	1	
	Hypertrophic scar	1	Infiltration
	Lymph fistula (post-stationary)	1	Surgical treatment
	Lymphocele (stationary)	1	Puncture
	Lymphocele (post-stationary)	1	Puncture
	Seroma (post-stationary)	3	Puncture (multiple times)
	Wound infection (stationary)	1	Antibiotics

Table 3 Donor side morbidity after lymph vessel transplantation

Complications overview lymph vessel transplantation			
Donor side	**Type**	**Quantity**	**Therapy**
	Lymph fistula (post-stationary)	2	Declining spontaneously, albumin substitution
	Lymphocele (post-stationary)	1	Puncture (multiple times)
	Iatrogenic lymphedema (post-stationary)	5	Compression garments
	Wound healing disorder (post-stationary)	1	Antibiotics
	Wound healing disorder with skin necrosis (post-stationary)	1	Surgical treatment
	Wound infection (stationary)	1	Antibiotics
	Wound infection (post-stationary)	1	Antibiotics

Previously, the same author had performed omental lymph node transplants in a laparoscopic manner with good results in ten patients[13]. Particular advantages of the robotic procedure were shown, among others, due to the three-dimensional image quality and the robot-supported preparation, which eliminates the physiological tremor and thus enables very precise and vessel-sparing preparation[12]. Due to the fact that abdominal lymph nodes are used for transplantation and the peritoneum is opened, a variety of potential complications arise with these procedures[14-18].

At present, only a few publications on robot-assisted VLNT have been published[12,19]. To the best of our knowledge, our study with n = 18 is the largest robot-assisted VLNT study published to date. In our patient group, 3/18 patients reported pulling pain in the abdominal and thoracic region within the first days after surgery. In our opinion, this is most likely due to the temporarily created pneumoperitoneum. The complaints had subsided after 12 d. Further complications have not occurred in our patient group so far. With regard to long-term complications such as trocar hernias and adhesions, no reliable assessment can be yet made.

Similar to other authors, we experienced some donor side morbidities after supraclavicular VLNT[20,21].

The unique reversible occurrence of Horner's syndrome in our group of patients illustrates the complex anatomy of the supraclavicular region, which has already been discussed before. In case of spontaneous regeneration, as in our event, it is assumed that the corresponding nerve was overstretched by retractors or inserted hooks during the operation[22].

Although several studies have already shown the general practicability of lymph vessel transplantation, there is little literature available on elevation defect morbidities. In addition to general complications such as wound infections, wound healing disorders and lymph fistula, five iatrogenic lymphedema occurred in the donor leg area. It should be noted that the listing in our study took place when compression garments were prescribed or recommended only once. We highly believe that the actual number of patients requiring compression garments will be much lower in the long run.

CONCLUSION

In summary, robot-assisted omental VLNT is clearly superior to supraclavicular VLNT and LVTx due to the reliably low donor side morbidity. The evaluation of long-term consequences will have to be clarified in future studies.

ARTICLE HIGHLIGHTS

Research background

Secondary lymphedema after surgery is a progressive, chronic disease that is still not completely curable. Over time a multitude of surgical therapy options have been described with its individual complications and side effects.

Research motivation

Due to technical progress in robot-assisted surgery, many advances have been made in this field within the last few years. This has significantly increased the precision and tissue-sparing work during abdominal interventions and made omental flap harvest much easier. Our motivation was to compare the complications of robot-assisted lymph node transfer in the treatment of secondary limb lymphedema.

Research objectives

Since 2010 we use the autologous supraclavicular lymph node transplantation (VLNT) and the lymph vessel transplantation (LVTx) according to Baumeister. Since 2017 we perform robot assisted free VLNT from the omentum. Our motivation was to summarize and point out the single-center complications in LVTx and free VLNT.

Research methods

In this study, data from three different collectives were collected and evaluated. A total of 87 patients undergoing treatment at our clinic were included. In total n = 18 robot-assisted omental lymph node transplantations, n = 33 supraclavicular lymph node transplantations and n = 36 Lymph vessel transplantations were analyzed. The data collection was performed preoperatively during consultations, as well as three weeks, six months and twelve months after surgical treatment. Descriptive statistics were used to analyze the patient data.

Research results

In the omental VLNT, three patients showed a slight abdominal sensation of tension within the first 12 postoperative days. No other donor side morbidities occurred. Our supraclavicular VLNT collective showed 10 lift defect morbidities with one necessary surgical intervention. In our LVTx collective, 12 cases of donor side morbidity were registered. In one case, surgical intervention was necessary.

Research conclusions

Concerning donor side morbidity, robot-assisted omental VLNT is clearly superior to supraclavicular lymph node transplantation and LVTx.

Research perspectives

At present, only a few publications on robot-assisted VLNT have been published. Because of the short time, no reliable assessment concerning long-term complications can be yet made. The evaluation will have to be clarified in future studies.

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