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PERSPECTIVE EXPERIMENTAL RESEARCH

The sentinel skin free flap in solid organ transplantation: patient perspectives

Matthew J Davies BMedSc BSc (Hons) MSurg 0000-0003-0813-4380,[1–3 a] Phaethon Karagiannis MBBS 0000-0003-4275-8197,[1] Elias Moisidis MBBS (Hons) FRACS (Gen) FRACS (Plast) 0000-0002-9746-9985,[1,2] Paul Jansz BMed FRACS PhD 0000-0002-4721-5549,[4] Vlad Illie MBBS (Hons) MS FRACS (Plast)[1,2]

[1] Department of Plastic and Reconstructive Surgery, St Vincent's Hospital, Sydney, AUSTRALIA. [2] Faculty of Medicine, University of New South Wales, Kensington, New South Wales, AUSTRALIA. [3] Macquarie University, Macquarie Park, New South Wales, AUSTRALIA. [4] Department of Cardiothoracic Surgery and Heart and Lung Transplant, St Vincent's Hospital, Darlinghurst, New South Wales, AUSTRALIA.

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Background

Transplant rejection is the greatest fear among both organ recipients and their treating team. It is a major source of morbidity and mortality in organ transplant recipients[1] and difficulty in establishing a timely and reliable diagnosis of rejection contributes to this burden. The use of a second allograft from the same donor, the sentinel skin transplant (SST), described as a free flap with a vascularised pedicle, simultaneously transplanted as a sentry for transplant rejection, has recently been developed.[2,3]

The utility of SSTs originates in their differing tissue composition compared with the lung or heart allograft. As they originate from the same donor, the overall rejection response is to the same genetic material; however, the immunological response varies based on the tissue type.[4] This offers a unique opportunity to exploit parts of this response in favour of the host. Skin, being an external organ, shows some visual signs of rejection which can be monitored by the patient constantly. Preliminary, limited findings suggest that these visual signs appear early in the rejection episode, correlate well with histological rejection and may improve diagnostic accuracy to avoid false diagnosis of rejection mimics and over-treatment.[5–7] This lead time will allow early management of rejection, which will reduce the impact on the primary transplant organ from each acute rejection episode, accumulating in improved transplant survival and organ function.[8] Accurate biopsy correlation between primary transplant and SST may also divert biopsies away from the primary transplant, offering a less invasive, complicated and risk-prone method for histological monitoring.[9] These benefits are the primary aim of the SST, however, the addition of a more immunogenic tissue type may increase the likelihood of allograft tolerance.[8] This may in turn reduce the need for or amount of chronic immunosuppressive medication and its impact on the patient's general health.[10]

[a] Corresponding author: Matthew J Davies BMedSc BSc (Hons) MSurg; Matt_davies@live.com.au

Aims of the study

It is clear then that SSTs offer an exciting avenue for potentially improved outcomes in a group that suffers significant morbidity and mortality. The unknowns will be whether these findings hold true in the long term and whether they have penetrance for solid organ transplant (SOT). In the interim, an evaluation of the acceptability of SST and the technical components is important to maximise uptake and eliminate additional concerns for the patient.

This study aims to understand the patient factors that may influence preoperative acceptance of an SST for heart and/or lung transplant recipients. This is with the intention of informing the preoperative discussion with patients planned for SST in the future and to guide further research in this domain. This research group has established itself with the intention of carrying out SST for heart and lung transplant recipients in due course.

Patients and methods

Patients who met criteria for this study had received either a heart or lung transplant. Fifty non-consecutive inpatients on the transplant ward at St Vincent's Hospital, which is the only heart and lung transplant centre in the state of New South Wales, Australia, were surveyed over a 12-month period, and gave consent for the study.

A questionnaire was provided to patients to gather information about their transplant, including date of surgery, type of transplant, number of biopsies and rejection episodes and complications from biopsies, willingness to accept SST (yes/no), concerns about SST (both in general and specifically cosmesis, religious, cultural, stigma issues) and foreseeable benefits of SST (both in general and in relation to reassurance by visual monitoring and reduced emotional strain of the transplant). This questionnaire was developed in consultation with the surgical and medical transplant teams as well as the plastic surgery department at St Vincent's Hospital. Mode of administration was face-to-face in the inpatient environment using interpreters as required. A scripted verbal brief was given to the patients prior to the survey being conducted and patients were asked to then summarise the information given to them, as an assessment of understanding. A background and description of the SST was given in addition to our reasons for performing the survey, including photos of forearm free flaps. Risks and benefits were discussed, including flap failure, increased rejection, increased immunosuppressives, non-concordant rejection, poor cosmesis, infection, bleeding, vascular injury and unforeseen short or long-term complications relating to this novel operation. Patients then underwent the survey about their willingness to theoretically accept an SST and any factors they could foresee impacting this decision. An assessment of the patient was made to determine any operative factors, including contraindication to radial forearm free flap (RFFF), using Allen's tests.

Ninety-five per cent confidence intervals were reported. This project received ethics approval from the St Vincent's Hospital Ethics Committee [2020/ETH01348] and was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007). This project complies with the principles of the Declaration of Helsinki formulated by the World Medical Association, the Declaration of Istanbul and the ISHLT Statement on Transplant Ethics.

Results

Fifty patients were included (M:F ratio 3:2) with a mean age at the time of survey of 56 (range 25–74, 95% CI 52.7 to 59.7). Mean time since transplant was 31 months (range 0–219 months, 95% CI 15.1 to 47.9). Most patients were heart transplant recipients (62%), with smaller numbers of lung transplant (32%) and heart-lung transplant (6%).

After a discussion of the risks and benefits of the procedure, as discussed above, we found that all patients surveyed indicated to us they would have been happy to receive an SST at the time of their initial transplant. Small numbers of patients advised us that despite concerns about cosmesis (18%) and potential stigma (4%), they still would opt for an SST. Particular note must be made of two patients who had very dark skin tone (one from Nigeria, another from Thailand), who made it clear that they would be keen to receive an SST despite an almost certain skin tone mismatch and poor cosmesis. No patients expressed any religious or cultural concerns.

Almost all patients (98%) felt that visual monitoring of rejection would decrease the emotional strain of organ transplantation. Almost all patients (98%) would feel reassured by a visual monitor of transplant rejection. Ninety-two per cent of patients had undergone allograft biopsy with a mean of 8.2 biopsies per patient (range 0–30, 95% CI 6.2 to 10.2) with 13 per cent having complications from these biopsies. Fifty-eight per

cent of patients had experienced some form of rejection.

Patients generally had normal Allen's tests with only a small number having Allen's tests that were abnormal bilaterally (6%).

SST as a monitoring tool

Early recognition and management of rejection is critical. Early treatment can not only halt progression into acute failure, but also helps avoid recurrent rejection episodes which cumulatively contribute to chronic failure.[11–13] Symptoms of rejection are often vague and can be confounded by heavy immunosuppression, major surgery and polypharmacy.[14–16] While routine biopsy regimes of the allograft remains the gold standard for monitoring, diagnosis and grading of rejection, acknowledging the risk of this invasive procedure to the allograft and to the patient is important.[17] Further, interpretation of the histological findings is not simple, particularly in the setting of other coexistent pathology.[18] It is particularly difficult to differentiate between infection and rejection by lung transplant biopsy. Alternatives to allograft biopsy, such as cardiac MRI, remain insufficient and rejection can develop between scheduled biopsies or scheduled alternative testing, no matter how frequent.[6]

It is known from experience with vascularised composite allografts (VCAs) for face or limb transplant, that of the transplanted components (skin, fascia, muscle, bone, vessels), the skin is particularly susceptible to rejection.[3] Multiple factors make allograft skin particularly prone to rejection. These include mode of revascularisation, lymphatic drainage and the role of skin as an immunologic effector.[4] The use of an SST transplanted distant to the VCA as a sentry for transplant rejection has recently been developed[2,3] and has shown earlier and more severe rejection episodes in both animal and human studies.[6,7] The visual skin changes that suggest rejection seem consistent and have been shown to reliably predict histological rejection.[7] This allows early non-invasive visual identification of rejection which may provoke formal biopsy diagnosis or even prompt immediate management.

Consistent and representative biopsy results may allow scheduled/routine biopsies to be redirected to the SST from the primary allograft to preserve cosmesis or function.[9] Early diagnosis and management of acute rejection, facilitated by the SST, may therefore delay or prevent chronic rejection and allograft failure. Every patient involved in the study felt particularly positive about using an SST as a monitoring tool and felt they would gain significant reassurance from this. Given such high rates of acceptability in this post-transplant case series, it was not feasible to stratify between heart vs lung recipients or between those admitted with rejection or with biopsy complications and other patients. Rejection phenomena are perceived as greater in lung transplant so these patients may have more to gain from sentinel flap monitoring. Those who have experienced rejection or biopsy complications may also be more accepting. This needs focused evaluation in future studies.

There is limited experience in the literature to suggest there are benefits with the use of SSTs in the context of SOT. Abdominal wall transplantation is a complex method for abdominal closure and in the setting of abdominal organ transplant recipients, doubles as an SST. The additional tissue burden is far greater in this context compared with the aforementioned SSTs for VCAs, as the abdominal wall transplants are much larger in size. However, the correlations between visual signs and histological findings and the consistency between the primary allograft and the SST remain.[8]

When receiving a transplant, a trade-off is made between transplanting an organ to cure end organ failure and introducing indefinite immunodeficiency to fight its rejection. While the addition of more allograft tissue naturally raises concerns about increasing rates of rejection, the use of SSTs may actually promote allograft tolerance.[8] Sentinel skin transplants have been shown to have no negative effects on the rate or severity of rejection episodes in animal studies.[7] Promisingly, the use of abdominal wall transplants as an SST for abdominal SOT significantly reduces the rate of rejection, aids in avoiding misdiagnosis and over-treatment of rejection mimics and improves graft survival, without alteration of the immunosuppressive regimen.[7,8 8]

All of the patients were happy to accept any foreseeable negatives even with the understanding of the limited evidence for potential benefits. They were also cognisant of the fact that SSTs for heart or lung transplants had not been done previously and could lead to unforeseen negatives. The collective altruism of transplant patients was obvious during our patient interactions, with many commenting that they would happily accept an uncertain risk profile if it meant furthering the field of transplant medicine. The psychological impact as a whole is,

however, unknown. Some patients, particularly younger patients, may not want an easily visible reminder of their transplant or may struggle to cover up their SST if they chose to do so. This may in fact add to the emotional burden, real or perceived. However, patients in this study nearly ubiquitously agreed that an SST would offer reassurance and reduce their emotional strain.

The cosmetic impact, although not enough to sway any patient decisions in this study, is still an important consideration. Differing skin tone is likely and may at times be significant as it would have been in some patients in this cohort. Inset site will be chosen on multiple factors including cosmesis, vascular anatomy and surgeon preference; the volar forearm inset of a donated radial forearm free flap (RFFF) is most likely. The RFFF is a robust, thin flap which offers reliable anatomy for procurement, adequate vessel calibre and pedicle length and is familiar territory for most microsurgeons. However, for younger or more cosmetically sensitive patients, alternative recipient sites, including the medial arm or posterior leg, may be explored.

As visual monitoring will play a large role in the immediate utility of SSTs, understanding the skin changes and educating staff and patients adequately will be essential. Interpreting these changes among other symptoms of rejection will require medical input, so a mechanism for early consultation and review by the transplant team must be established. The accuracy of interpreting skin changes will improve over time and it is important that this knowledge is shared and reviewed regularly. Artificial intelligence may eventually play a role as a tool to assess the visual changes of rejection—to avoid false positives and reassure patients. This may also allow telehealth to play a role with frequent reviews of the SST or even SST punch biopsy collection being feasible from afar, potentially by a trained nurse or doctor. This is particularly important in the Australian context where patients often travel many hours for regular reviews by their transplant specialists.[19]

Technical limitations will need to be addressed in consultation with the transplant team. Using an SST in the setting of distant procurement, using 'heart in a box' technology, may not be feasible. The presence of two teams operating in close proximity during organ procurement and inset, including the use of a microscope, will be challenging. The teams will need to coordinate the use of heparin and onset of ischaemic time, among other potentially competing interests. Patient selection for SST will also need to be strict, with an evaluation of risks for flap failure including peripheral atherosclerotic disease, which are higher in transplant patients.[20] Poor wound healing is a well-known complication of immunosuppression, so particular attention must be taken to optimise healing, including fastidious haemostasis, aseptic technique, reducing tension and a strict postoperative observation regimen.[21]

These findings must be interpreted in the context of likely publication bias given that experience is limited, and this approach is certainly not common practice. Patients are naturally overwhelmed in the workup for organ transplant and consent for procedures of this nature is complex. The added complexity to the operation and perioperative period, potential new complications and limited evidence to suggest benefit need to be carefully discussed with the patient and their family. New issues are likely to arise during the early adaptation of this strategy and should be routinely assessed. Clinicians should be mindful of their bias and optimism and openly present the known research findings and theoretical advantages.

This study will inform patient selection, preoperative discussions and operative planning for future studies implementing SSTs in heart and lung transplant recipients at this centre. This study is limited by small patient numbers, limited scope and its largely qualitative nature. This is a non-consecutive series of inpatients, so there is inherent, although likely small, potential for selection bias. Future work will survey patients on the transplant waiting list as acceptability may differ after receiving the gift of transplantation.

Conclusion

Sentinel skin transplants have the potential to significantly alter the landscape of transplant medicine. Limited but promising evidence exists for the benefits of SSTs in the setting of VCAs and abdominal organ transplant. Allograft skin demonstrates early and reliable changes in acute rejection. Offering a lead time and improving diagnostic accuracy may improve short- and long-term outcomes. Allograft tolerance may also be improved with the addition of skin to the transplant load. The application of SSTs to SOT will open up these benefits to the majority of transplant recipients. This study demonstrated that SOT patients are accepting of any potential risks or complications associated with the SST. Patients predict SST would provide reassurance and reduce the emotional strain of organ transplant and potential rejection.

Patient consent

Patients/guardians have given informed consent to the publication of images and/or data.

Conflict of interest

The authors have no conflicts of interest to disclose.

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