Canadian survey on the rates of use of intraoperative diuretics and justification for their use during renal allograft reperfusion

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Background: Mannitol and furosemide have been used as diuretics intraoperatively to facilitate early renal allograft function and reduce delayed graft function. As the evidence of any efficacy of these agents is limited, we sought to characterize the use of diuretics among transplant surgeons.

Methods: An anonymous online survey was sent to all Canadian transplant programs where kidney transplants are routinely performed. Questions were related to the use and indications for mannitol and furosemide. Responses were collected and analyzed as counts and percentages of respondents. We used χ^2 analysis to assess the relationship between demographic factors and survey responses.

Results: Thirty-five surgeons completed the survey (response rate 50%). Seventy per cent of respondents reported performing 26 or more transplants per year, 88% had formal transplant fellowship training and 67% indicated that they currently train fellows. Only 24% and 12% reported believing that delayed graft function is reduced by mannitol and furosemide use, respectively. However, 73% routinely gave mannitol to patients and 53% routinely gave furosemide. The most common justification given for mannitol use was to induce diuresis (54%); 37% of respondents reported using mannitol because of training dogma. Likewise, 57% used furosemide for diuresis, with 23% reporting that their use of this agent was based on dogma. No relationship emerged between fellowship training, case volume or training program status and the use of any agent. Interestingly, 71% of respondents indicated that a randomized controlled trial evaluating the utility of intraoperative diuretics is needed and that they were interested in participating in such a trial.

Conclusion: Use of intraoperative diuretics and the rationale for their use vary among surgeons. A substantial proportion of surgeons use these medications on the basis of dogma alone. A randomized controlled trial is needed to clarify the role of intraoperative diuretics in kidney transplant surgery.

Contexte : On a utilisé le mannitol et le furosémide comme diurétiques peropératoires pour stimuler le fonctionnement précoce de l'allogreffe rénale et réduire le retard de fonctionnement du greffon. Comme les données probantes quant à l'efficacité de ces agents sont limitées, nous avons voulu caractériser l'utilisation des diurétiques chez les chirurgiens qui effectuent ces transplantations.

Méthodes : Un sondage anonyme en ligne a été envoyé à tous les programmes de greffe canadiens où des greffes rénales sont couramment effectuées. Les questions avaient trait à l'utilisation et aux indications du mannitol et du furosémide. Les réponses ont été recueillies et analysées sous forme de nombres et de pourcentages des répondants. Le test du χ^2 a été utilisé pour évaluer le lien entre les facteurs démographiques et les réponses au sondage.

Résultats : Trente-cinq chirurgiens ont répondu au sondage (taux de réponse 50 %). Soixante-dix pour cent des répondants ont indiqué effectuer annuellement 26 greffes ou plus, 88 % avaient suivi une spécialisation formelle pour l'exécution des greffes et 67 % ont dit être en cours de spécialisation. Seulement 24 % et 12 % respectivement ont dit croire que le mannitol et le furosémide permettent de réduire le retard de fonctionnement du greffon. Toutefois, 73 % et 53 % respectivement administraient de routine du mannitol et du furosémide aux patients. La justification la plus fréquente de l'utilisation du mannitol était d'induire la diurèse (54 %); 37 % des répondants ont dit utiliser le mannitol parce que c'est ce qu'on leur a enseigné durant leur formation. De même, 57 % utilisaient le furosémide pour la diurèse, dont 23 % disaient que c'est ce qu'on leur avait enseigné durant leur formation. Aucun lien n'est ressorti entre la

spécialisation, le volume de cas ou le statut à l'égard du programme de formation et l'utilisation d'un agent quelconque. Fait à noter, 71 % des répondants ont indiqué qu'un essai randomisé et contrôlé sur l'utilité des diurétiques peropératoires serait nécessaire et qu'ils y participeraient volontiers.

Conclusion : L'utilisation de diurétiques peropératoires et la justification de leur utilisation varient d'un chirurgien à l'autre. En majeure partie, les chirurgiens utilisent ces médicaments sur la base des notions théoriques seulement. Un essai randomisé et contrôlé s'impose pour clarifier le rôle des diurétiques peropératoires dans la greffe rénale.

Renal transplantation remains the preferred treatment for the management of end-stage renal disease.[1] Despite high technical success rates for the procedure, transplanted kidneys can experience slow or delayed graft function, leading to longer stays in hospital, increasing costs and potentially worse long-term graft outcomes.

Delayed graft function (DGF) is a clinical condition commonly defined in the modern era as requiring dialysis within the first week of receiving a kidney transplant, and it is largely attributed to ischemia–reperfusion injury.[2] Aside from the drawback of the requirement for mechanical renal replacement in the immediate posttransplant period, DGF has been associated with higher rejection rates; intervention to attenuate this process may reduce costs of transplantation as well as improve patient outcomes.[2] Several approaches have been taken to ameliorate DGF. Precise hydration protocols, preservation solutions, pulsatile perfusion devices, strategies to minimize warm and cold ischemic time, antibody-based induction agents and the use of intraoperative diuretics have all been incorporated into renal transplantation protocols to minimize the risk of DGF.[3–7] Both mannitol, an osmotic diuretic, and furosemide, a loop diuretic, have been used in contemporary practice as diuretics during transplant.

Current teaching indicates that diuretics should be administered intraoperatively around the time of graft reperfusion to improve early graft function. The method by which these agents may benefit a transplanted kidney is thought to relate to reducing the impact of ischemia–reperfusion injury via several purported mechanisms.[8–12] Observed improvements in renal function at a cellular or clinical level have largely occurred in basic science studies, with a dearth of literature supporting their role in contemporary human clinical contexts. A lack of studies demonstrating consistent benefit of intraoperative diuretics leads to variation in clinical practice.[13] Recently, it has been suggested in the literature that a prospective randomized controlled trial (RCT) is needed in this area.[13,14]

The purpose of this study was thus 2-fold. First, we sought to assess rates of diuretic use and the justifications for their use. Second, we sought to determine whether performance of a large-scale formal study of intraoperative diuretics would be meaningful enough to the transplant surgical community to justify such an undertaking. We conducted our study via an anonymous survey of surgeons involved in kidney transplantation. We hypothesized that survey respondents would report varying utilization of mannitol and furosemide and that they would demonstrate interest in an RCT examining the utility of these agents.

Methods

An anonymous online survey was sent to Canadian transplant surgeons (including urologists, general surgeons and multiorgan transplant surgeons) who currently perform kidney transplantation to assess the rates of utilization of mannitol and furosemide in the intraoperative setting during kidney transplant recipient surgery. We identified eligible surgeons by cross-referencing email lists and membership lists of transplant societies of which kidney transplant surgeons are members. All eligible surgeons were invited via email to participate. Approval was obtained from Western University's Health Sciences Research Ethics Board before initiation of the survey (IRB registration no. 00000940, study identification no. 112876).

A 24-item survey was distributed through the online Qualtrics survey software licensed by our institution. Survey items were created to gather nonidentifiable demographic information on topics including respondents' personal and institutional case volume, their formal fellowship training (if any) and their participation in ongoing training of fellows. The remaining survey items were designed to collect information on the respondents' use of mannitol, furosemide or both during recipient transplant surgery, as well as their opinions about whether either agent reduces DGF and the justification for use of each agent. The justification for the use of the diuretics was assessed via a survey item that allowed respondents to select from a list of purported mechanisms described in the literature. Finally, interest in a multicentre RCT was assessed by survey items asking whether respondents would find value in such a study, what outcomes would be of interest to them and whether they would be interested in participating in such a study.

Participants could complete the survey during a 1-month period, after which responses to survey items were collated; a reminder email was sent to all invited participants half-way through the survey period. Answers were

counted and converted to percentages of respondents. The relationship between demographic data and responses to diuretic use was assessed via cross-tabs of survey items, and χ^2 testing was used to identify if any individual factors were associated with trends in diuretic use. Analysis was completed using Qualtrics' embedded statistical software (Stats iQ) with an α of 0.05.

Results

The survey was completed by 35 respondents, for an overall response rate of 50%. Twenty surgical centres were represented in the survey. Table 1 shows the demographic characteristics of survey respondents. Sixty-eight percent of respondents had more than 5 years of transplant surgery experience, with 70% performing 26 or more cases per year. Eighty-eight percent of respondents had formal fellowship training in kidney transplantation surgery, and two-thirds reported that they currently participate in the ongoing training of transplant fellows at accredited transplant programs.

Seventy-three percent of respondents reported using mannitol routinely, 53% reported routine furosemide use and 58% reporting routine use of both diuretics (Fig. 1). However, only 24% believed mannitol reduces rates of DGF, while 12% believed furosemide may help reduce DGF. Interestingly, 37% of respondents justified the use of mannitol with the response "I was always taught to use it"; 23% justified the use of furosemide for a similar reason, and it was the second most common justification for both agents. The spectrum of rationales given for use of these agents is depicted in Figure 2.

Table 1. Characteristics of survey respondents

Characteristic	% of respondents $n = 35$
Years of kidney transplant surgery experience*	
0–5	26
6–10	23
11–20	31
> 21	14
Personal annual case volume	
1–25	30
26–50	43
51–75	21
76–100	3
101–150	3
Hospital case volume	
1–25	3
26–50	9
51–75	12
76–100	9
101–150	33
> 150	33
Fellowship trained	
Yes	88
No	12
Currently train fellows	
Yes	67
No	33

*The percentages in this category do not add up to 100% because 2 respondents did not answer this question.

When presented with survey items related to formal study of this topic in an RCT, most respondents indicated interest in participating in such a trial (71%). Outcomes of interest that would potentially lead to a change in or affirmation of practice from such a trial are displayed in Figure 3. The outcome that most interested respondents was determining whether diuretic use would lead to a reduction in DGF rates.

Statistical analysis failed to reveal any relationship between the respondents' demographic characterisitcs and their responses related to the use of mannitol, the use of furosemide or the justification for the use of these diuretics. None of the factors for personal case volume, institutional case volume, years of experience, formal fellowship training and current involvement in the training of fellows showed any predictive value regarding use of intraoperative diuretics (data not shown).

Discussion

Results from our anonymous survey of Canadian kidney transplant surgeons revealed heterogeneous utilization of mannitol, furosemide and in some cases both diuretics. Although most respondents reported that they use some sort of diuretic during transplant procedures, a sizeable proportion did not. This observation points to a lack of consensus in the transplant community on the utility of these agents and on their role, especially when they are considered in the context of other intraoperative medications such as induction immunotherapy, which is considered the standard of care in international guidelines through level 1 evidence.[1]

A lack of clear benefit in clinical contexts may account for the discrepant patterns of diuretic use. Mostly historical reports citing the benefits of mannitol in the clinical setting have driven its endorsement in transplantation. Van Valenberg and colleagues once described the intraoperative use of mannitol as "indispensable."[15] In their prospective RCT of first-time recipients of deceased donor kidney transplants, patients were randomly allocated to receive treatment with 250 mL of 20% mannitol or 250 mL of 5% dextrose solution in addition to an intraoperative hydration protocol. The authors found that rates of DGF, defined as less than 400 mL of graft-derived urine output in 24 hours and/or the necessity of dialysis during the postoperative course due to factors other than vascular occlusion or bladder/ureteric obstruction, were significantly reduced in the mannitol groups

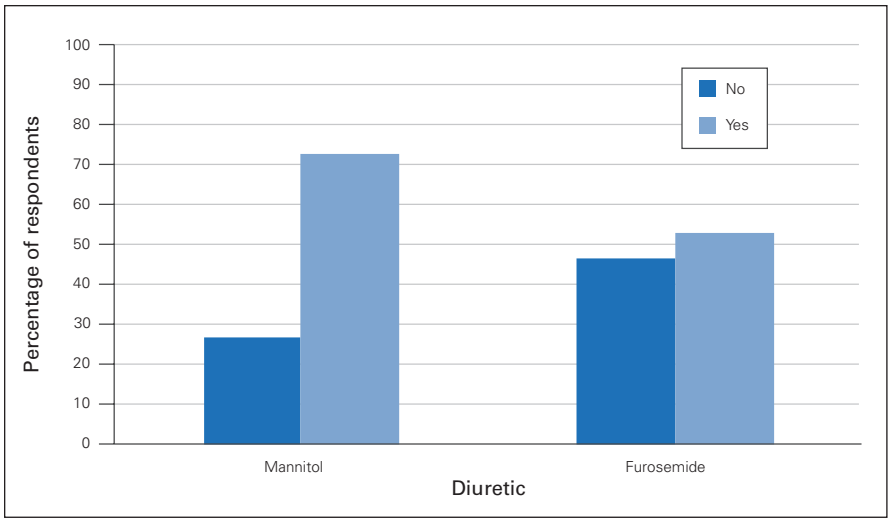

Fig. 1. Percentage of respondents reporting use of mannitol or furosemide.

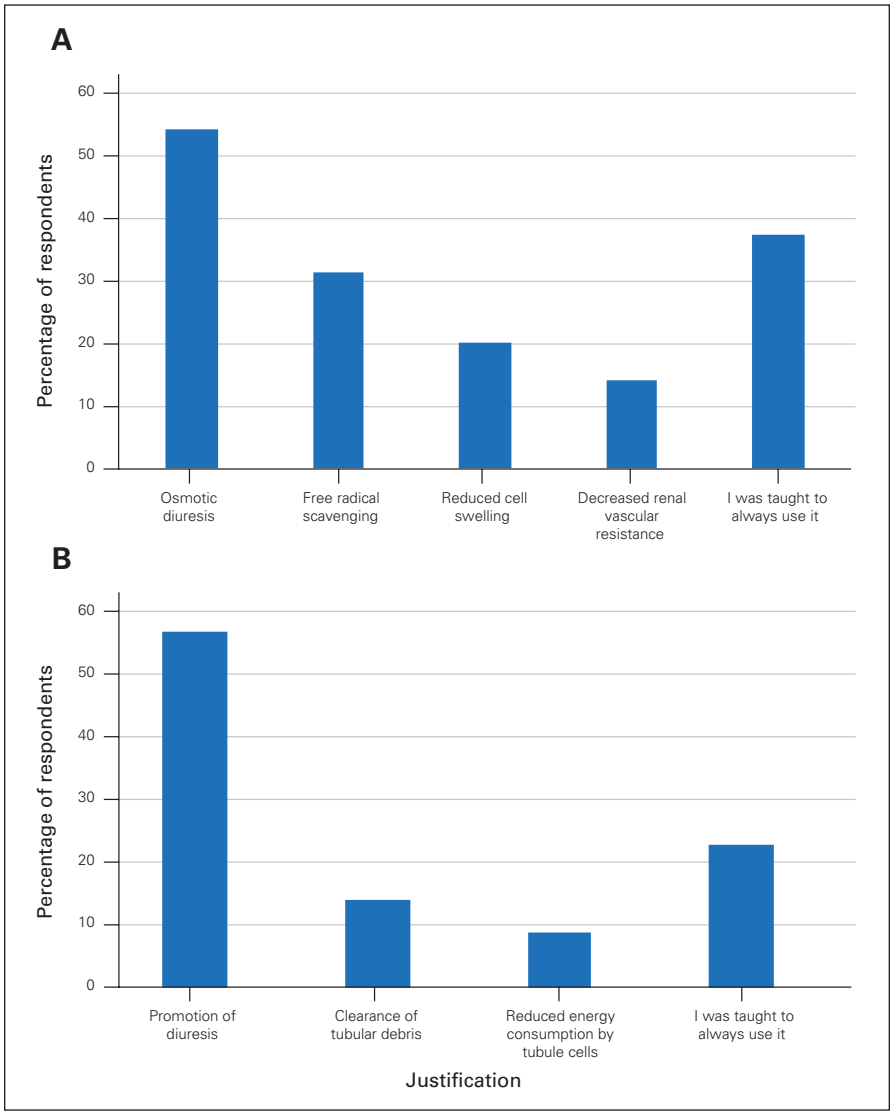

Fig. 2. Justifications given by respondents for the use of (A) intraoperative mannitol and (B) intraoperative furosemide during kidney transplant surgery.

(19% v. 53%).[15] Induction therapy was absent in this protocol, and calcineurin inhibitors were started within 6 hours of revascularization. Modern practices typically involve antibody-based induction therapy that may reduce rates of immune-mediated DGF and can allow for delayed initiation of calcineurin inhibitors.[16] Furthermore, hypothermic machine perfusion, known to reduce rates of DGF, is more commonplace in current practice.[7,17] The evolution of perioperative care and handling of deceased donor kidneys changes the baseline risk of DGF that may be influenced by diuretics. Nonetheless, the report by Van Valenberg and colleagues and other reports of a similar vintage have supported the ongoing use of mannitol for the prevention of DGF.[3,15]

In a European multi-institutional study, Koning and colleagues reported on rates of DGF in recipients of kidneys procured from heart-beating deceased donors and preserved with either EuroCollins or University of Wisconsin solution maintained on static cold storage; the use of induction immunotherapy was not specified.[4] Stepwise logistic regression analysis identified recipient and donor factors associated with DGF. The use of intraoperative mannitol was found to be associated with reduced rates of DGF in univariate analysis of this cohort (21% v. 30%, $p = 0.03$). However, when mannitol was considered in a multivariate model, its predictive value for DGF was lost.[4] Interestingly, the use of mannitol was recommended to participating recipient surgeons as part of the research protocol, but 30% of recipient patients did not receive mannitol. This may suggest uncertainty among participating surgeons even 2 decades ago.

Although these older studies marginally support the use of intraoperative mannitol, contemporary studies have failed to demonstrate benefits. In a single-centre retrospective review, Hanif and colleagues compared the outcomes of transplant recipients who

received intraoperative diuretic versus none. Overall rates of DGF and graft survival at 1 year were similar between groups. However, the generalizability of the study's findings is limited by the lack of randomized design and the study's use of a more lenient definition of DGF.[13]

The evidence supporting use of furosemide as a single agent is lacking as well. In a review of the literature, Schnuelle and van der Woude noted that loop diuretics have not been shown to affect DGF or improve outcomes.[2] In a comprehensive review of the literature examining studies using loop diuretics in kidney transplant, Sandal and colleagues found an overall lack of consistent clinical efficacy.[14] No randomized or prospective studies in the literature evaluating loop diuretics showed benefit, with lack of effect on preventing acute tubular necrosis, rates of immediate graft function and rates of forced diuresis compared with other agents.[14]

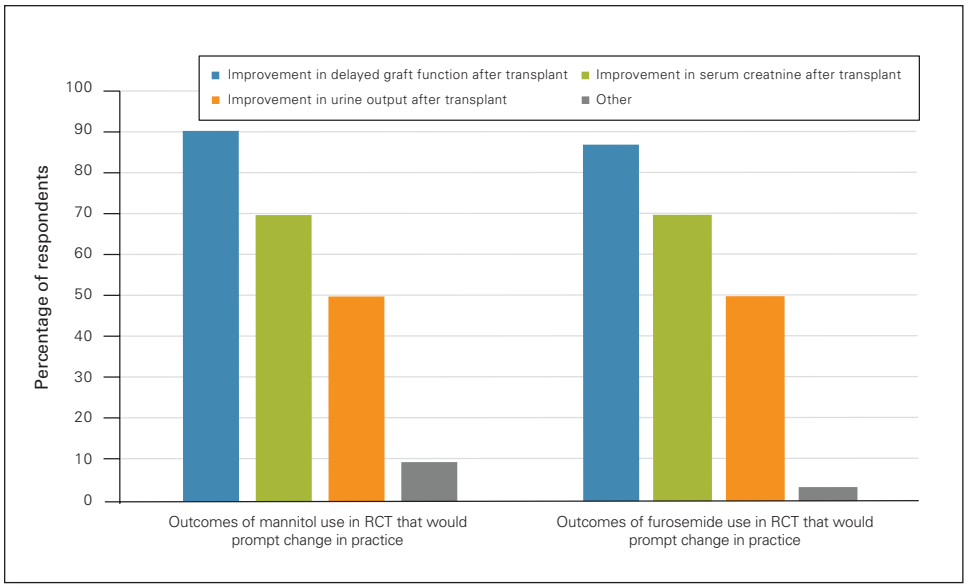

Fig. 3. Reported outcomes of a randomized controlled trial (RCT) examining mannitol and furosemide use during kidney transplant surgery that would prompt a change in respondents' practice.

Diuretic administration to ameliorate ischemia–reperfusion injury to the kidney has a history in other renal surgical contexts. The use of intraoperative mannitol during partial nephrectomy for malignancy, a related practice perpetuated by dogmatic teaching, has also recently come under scrutiny. Spaliviero and colleagues reported on a recent RCT that compared the renal function outcomes of patients undergoing partial nephrectomy randomly allocated to receive treatment with either mannitol or placebo administered within 30 minutes of hilar clamping. These authors found no difference in clinically detectable renal function recovery after partial nephrectomy, and they subsequently called for the practice of intraoperative mannitol administration to be abandoned.[18]

An online survey of European transplant centres was performed by Hanif and colleagues that included a 4-item questionnaire on whether participating surgeons routinely used mannitol, furosemide, a combination of both mannitol and furosemide, or no diuretic.[13] Of the 40 respondents, 13 (33%) reported no diuretic use in transplantation, 10 (25%) used mannitol, 6 (15%) used furosemide and 11 (28%) used a combination. The results of our survey showed a similar trend, albeit with different rates of diuretic use. These authors, and others, indicate a need for a well-designed RCT to clarify the role of intraoperative diuretics.[13,14] The present study goes beyond the results of Hanif and colleagues. Our survey administered 26 items that provide insight into rates of use as well as the justification for the use of both mannitol and furosemide. We show that Canadian transplant surgeons vary in their choice of intraoperative diuretics as well as whether to even use them. These use patterns appear to be independent of years in practice, having gone through formal fellowship training, case volume or participation in ongoing fellow training. The majority of surgeons suggested that current practice was based on surgical dogma. We agree with other published reports that a large, well-designed RCT is needed to define an evidence-based role for intraoperative diuretics in contemporary transplant surgery.[13,14]

The strengths of the current study relate to the modern, comprehensive characterization of diuretic use and justification. Furthermore, the survey enjoyed a high response rate, and probably all surgeons performing kidney transplant in Canada were invited to participate.

Limitations

Limitations of this study include the lack of data on dosages used, whether bolus or infusions of diuretics are commonly administered, and the inability to distinguish scenario-specific use of diuretics. Furthermore, the mix of urologists versus general surgeons among respondents was not captured. The inherent biases of these 2 surgical groups may affect their decision-making around intraoperative diuretic use. It is also possible that some Canadian surgeons were inadvertently not invited to participate; however, we consider this to be unlikely. Despite these factors, we believe our results provide a relevant snapshot of the current state of diuretic use, and it is clearly heterogeneous.

Conclusion

The findings of this study indicate that the use of mannitol and furosemide in kidney transplant recipient surgery is variable, and it is partially based on tradition and dogmatic teaching. There is strong interest in the outcomes of a well-designed RCT investigating this topic. Further study in this area is warranted.

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