Can furosemide prevent transfusion-associated circulatory overload? Results of a pilot, double-blind, randomized controlled trial

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BACKGROUND: Transfusion-associated circulatory overload (TACO) is a leading cause of transfusion-attributable morbidity. It is unclear whether diuretics are safe and effective in preventing this reaction.

MATERIALS AND METHODS: In a pilot controlled feasibility trial, inpatients 65 years or older ordered a single unit of red blood cells were randomized to pre-transfusion furosemide 20 mg or placebo intravenously. Primary outcome was the ability to enroll 80 patients within a 2-month time period. Secondary feasibility outcomes included proportion of RBC transfusions meeting eligibility criteria, proportion of eligible patients enrolled, and compliance to study protocol. Clinical outcomes included the incidence of TACO and associated complications.

RESULTS: Nine months of enrollment were required for 80 patients to complete the study, due primarily to fewer transfusions than expected meeting eligibility criteria and lower than anticipated consent rates. Protocol compliance was below target due to missing chart documentation of patient fluid balance, and transfusion infusion time. Blinding was maintained throughout the study and treatment arms were well-balanced. A single case of TACO occurred in each arm, for an overall incidence of 2.5%. No differences in peri-transfusion vital signs, B-natriuretic peptide, or signs of furosemide toxicity were observed.

CONCLUSION: The study protocol was not feasible as designed, primarily due to challenges in patient enrollment. Modifications to trial design to improve feasibility in future studies have been identified.

Transfusion-associated circulatory overload (TACO) is a common but under-reported complication of transfusion therapy, and is associated with significant morbidity and mortality.[1,2] The incidence varies per patient population, monitoring protocol, and diagnostic criteria used; recent studies have reported TACO rates of 3% of perioperative patients to 11% in critically ill patients.[3,4] Within international hemovigilance databases, TACO now accounts for 20% of all transfusion-related deaths reported in United States,[5] 32% of transfusion-related deaths reported to Health Canada[6] and 60% of transfusion-related deaths in the United Kingdom.[7] Elderly patients >65 years of age and those with a history of cardiac or renal disease are at particularly high risk.[3,8]

While pre-transfusion furosemide has been evaluated in neonates,[9] to date there have been no studies to determine which interventions reduce the incidence of TACO in adults.[10] Common recommendations include the use of single unit RBC transfusions, the selection of lower-volume alternatives where applicable (e.g., prothrombin complex concentrates rather than plasma for warfarin reversal), and slowing infusion rates.[2,11] Furosemide may decrease the risk of TACO, both through its known diuretic effect[12] and, potentially, by its ability to venodilate.[13] Although small studies have demonstrated that furosemide can blunt transfusion-associated increases in pulmonary capillary wedge pressure,[14] practice guidelines have not yet endorsed its use in preventing TACO, due in part to concerns of its potential to cause

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electrolyte disturbances and hypotension.[11] Accordingly, the use of pre-transfusion furosemide varies significantly between physicians and institutions, even in high-risk patients.[14,15]

A recent Cochrane meta-analysis has concluded that there is an urgent need to determine the therapeutic utility of pre-transfusion diuresis, preferably through the conduct of a randomized-controlled trial.[9] Given the significant morbidity and mortality caused by TACO, and the presence of clinical equipoise regarding the efficacy of furosemide in preventing it, we performed a pilot randomized controlled trial to determine the feasibility of performing a definitive multi-center study.

MATERIALS AND METHODS

Patients

Patients were enrolled at two academic acute-care hospitals in Toronto, Canada (University Health Network and Sunnybrook Health Sciences Centre). Research ethics board approval was obtained at both participating sites and all subjects gave written informed consent. Eligible patients were inpatients aged 65 years or older who were ordered a single unit of red blood cells (RBCs) outside of the operating or trauma room setting, during regular working hours (Monday–Friday, 8:00 am to 5:00 pm). Screening was performed within the blood bank by the technologists upon the receipt of a request to issue RBCs; if the order met the above criteria, the study coordinator was notified and the patient and their caregivers were approached for a more detailed assessment of inclusion and exclusion criteria. In addition, an automated script was implemented within the blood bank information system which sent an email to the study coordinator whenever a single unit of RBCs was prepared for an inpatient aged 65 years or older; if the orders originated during regular working hours and were for inpatients outside of the operating room, the patient and their caregivers would be approached to confirm eligibility. Exclusion criteria included: a concurrent order for platelet or plasma transfusion; serum sodium <130 mmol/L, serum potassium <3.5 mmol/L, an estimated glomerular filtration rate <30 mL/min•1.72 m^2 or on dialysis; active bleeding (as reported by the patient's clinical team or as evidenced by a hemoglobin (Hgb) decrease ≥20 g/L within the past 24 hours); surgical procedure performed or anticipated within 24 hours of transfusion; systolic BP <90 mmHg or inotrope-dependence; palliative status; planned same-day discharge; or previous enrollment in this study. After reviewing detailed eligibility and screening criteria from July 13 to November 3, 2016 and following review by the Data Safety Review Board (DSMB), a baseline potassium of 3.0–3.4 mmol/L was allowed if 40 mEq of potassium chloride supplementation was administered at the time of study intervention.

Treatment

Patients consenting to enrollment were randomized to receive either pre-transfusion furosemide 20 mg IV (defined as administration no more than 60 minutes before the start of transfusion) or an equal volume of normal saline. The randomization to either furosemide or placebo was generated by hospital research pharmacy staff using a computer-based randomization program, with allocation assigned in a 1:1 ratio in randomly permuted block sizes of four to six. Study syringes containing 2 mL of either furosemide or normal saline were then drawn up based on this randomization code. To stratify by center and renal function, the research pharmacy of each participating site would sequentially number syringes in two groups: one for patients with GFR 30–59 and one for those with GFR ≥60 mL/min/1.73 m^2). When a patient consented to randomization, the study coordinator of each site would request a sequentially numbered study drug syringe from pharmacy based on the patient's current GFR. However, study coordinators and patients remained blinded to the randomization code, which was only revealed by research pharmacy at the end of the study. To decrease waste, only five syringes of study drug were made up at a time and all were refrigerated and stored within an opaque bag for up to 14 days prior to use.

Informed consent was obtained by study personnel prior to the start of transfusion and the collection of any baseline laboratory tests not already performed as part of routine care. The great majority of patients had baseline hemoglobin, electrolyte, and plasma creatinine results already available through routine care to confirm enrollment eligibility, but additional venipuncture was required to obtain baseline B-type Natriuretic Peptide (BNP) levels.

The study treatment was prepared by hospital pharmacy and provided to study personnel as 2 mL injectable syringes that could either be administered by direct IV push or added to a 50 mL mini-bag of normal saline, administered by gravity infusion. Patients receiving regular treatment with diuretics were allowed to continue them in addition to their assigned study treatment. Patients who had been prescribed diuretics with their transfusion, however, could only participate in the trial if their physician believed there was clinical equipoise for their patient to participate and believed it was safe to cancel the furosemide order prior to randomization. No other changes to patient management were mandated by the study protocol: rates of product infusion, administration of other intravenous fluids, and treatment of any adverse transfusion reactions remained at the discretion of the patient's clinical team. However, pre-study institutional guidelines encouraged the infusion of RBCs to inpatients at a rate of one unit over 2–4 hours, and the suggested investigation of adverse respiratory events included both a clinical volume assessment and imaging by chest x-ray. Choosing Wisely Canada recommendations for RBC transfusion (e.g., avoidance of transfusion to asymptomatic patients with hemoglobin >70–80 g/L and the use of single unit transfusions for non-bleeding inpatients) are also actively promoted at both study sites. [16]

Follow-up

Baseline patient characteristics recorded included demographics, medical history including previous diagnoses of cardiac

or renal disease, and the use of any long-term diuretic therapy. As part of the follow-up protocol, patients had vital signs performed (including oxygen saturation by oximetry and, if available, central venous pressure) at the following intervals: pre-transfusion, 15 minutes after the start of the transfusion, at conclusion of transfusion, 6 hours (±2 hours) after the completion of transfusion, and with any suspected adverse transfusion reaction occurring within 24 hours after the completion of transfusion. In addition, the following laboratory tests were performed pre-transfusion and on post-transfusion day one (at 12–30 hours after a completed transfusion): complete blood count, serum sodium, potassium and creatinine levels, and B-type natriuretic peptide (BNP). 24-hour fluid balance the day following transfusion was also recorded, as were the results of any chest imaging performed. All patient assessments, laboratory tests, and imaging studies were performed by non-study clinical personnel; patient charts were subsequently reviewed by study coordinators for the purposes of data extraction. This chart review also included a search for documented change in positive pressure ventilation, inotropic or vasodilatory support, or any additional diuretic within the 24 hours following completion of transfusion. Charts were reviewed again at day seven (or following discharge if that occurred earlier) for the results of any echocardiography performed post-transfusion, documentation within the chart that the patient had developed an acute coronary syndrome or arrhythmia following the transfusion, or any evidence that the patient had received treatment for post-transfusion hyponatremia, hypokalemia, hypotension, or acute kidney injury. Patients were assessed for mortality for up to 30 days during their inpatient stay.

Outcomes

The primary feasibility outcome for the trial was the ability to enroll 80 patients within a 2-month time period, as mean enrollment at a rate less than 20 patients per month per institution would suggest significant difficulties would be encountered in completing an adequately-powered, large-scale clinical trial. Secondary feasibility outcomes included the proportion of RBC orders screened meeting eligibility criteria (target ≥10%), the proportion of eligible patients consenting to participate (target ≥25%), the proportion of consenting patients receiving the allocated treatment (target ≥90%), the proportion of randomized patients completing study follow-up protocol (target ≥80%) and the proportion of randomized patients for whom blinding was maintained (target 100%). Loss of blinding was defined as inadvertent disclosure by research staff in the hospital pharmacy, as reported by either study personnel or the patient's clinical team, whether the active treatment or placebo had been issued. Due to slower than anticipated enrollment, monitoring the proportion of institutional RBC orders that met all enrollment criteria was only performed from July 13 to November 3, 2016, so as to allow greater resources to be dedicated to trial recruitment.

The primary clinical outcome recorded was the development of TACO, using criteria adopted from the US Centers for Disease Control,[17] namely any three of the following six criteria, occurring within 6 hours of transfusion unless otherwise stated:

1. Acute respiratory distress (patient reported symptoms of dyspnea, orthopnea, or cough; fall in oxygen saturation (SpO2) ≥5%; or increased oxygen requirements)
2. BNP elevation of ≥50% above baseline, obtained within 30 hours of transfusion
3. Central venous pressure (CVP) above institution upper limit of normal, obtained within 24 hours post-transfusion
4. Evidence of left heart failure as defined by either:
   a. documentation of clinical examination findings consistent with the diagnosis of heart failure (e.g., elevated JVP, gallop rhythm or S3, pulmonary crackles)
   b. systolic BP increase ≥30 mmHg above baseline within 6 hours post-transfusion
5. Positive fluid balance at 24 hours post-transfusion
6. Radiologist report consistent with pulmonary edema (e.g., interstitial infiltrates, Kerley B lines, vascular redistribution, peri-bronchial cuffing)

Severity of TACO was graded as per the Canadian Transfusion-Transmitted Injuries Surveillance System as non-severe, severe, life threatening, or death.[6] As a potential surrogate marker for TACO, patients were also assessed for an increase in systolic blood pressure ≥30 mmHg from baseline within 24 hours of transfusion. Secondary clinical outcomes documented included: change in vital signs immediately post-transfusion and at 6 hours post-transfusion (including change in positive end-expiratory pressure at 6 hours post-transfusion amongst patients receiving mechanical ventilation); any other adverse transfusion reactions reported or meeting TTISS criteria within 6 hours of completing transfusion; net fluid balance at 24 hours from start of transfusion; need for increased supplemental oxygen, positive pressure ventilation, inotropic support or additional diuretic, or vasodilatory therapy within 24 hours; the occurrence of an acute coronary syndrome or new arrhythmia within 7 days; mortality during hospital stay; and length of hospital stay.

Outcomes potentially indicating toxicity from furosemide were assessed at 24 hours post-transfusion and included changes in serum sodium (with hyponatremia defined as <130 mmol/L) and potassium (with hypokalemia defined as <3.0 mmol/L), creatinine (with acute kidney injury defined as an increase ≥33% in serum creatinine from baseline) and hypotension (defined as a fall in systolic BP ≥30 mmHg from baseline). Other suspected adverse reactions reported by the patient's clinical team were also documented and classified as per Common Terminology Criteria for Adverse Events.[18] A DSMB comprised of a critical care specialist, nephrologist, and cardiologist was established for the purpose of reviewing safety and feasibility data provided by the investigators after 10, 40, and 80 study participants had completed follow-up, and in response to

study-related serious adverse events or other reported concerns regarding patient safety. Specific stopping rules were not defined but the DSMB was given the authority to terminate the study if it identified significant feasibility or safety issues.

Descriptive statistics were calculated using means with standard deviation for continuous variables (medians and interquartile ranges for non-normally distributed variables) and counts and percentages for categorical variables. All analyses were run using SAS Version 9.4 (SAS Institute). This trial was registered with ClinicalTrials.gov Identifier NCT02802696.

RESULTS

Enrollment began at Sunnybrook Health Sciences Centre on July 13, 2016 and at the University Health Network (Toronto General and Princess Margaret Hospital sites) on July 22, 2016. Although these two institutions collectively transfuse approximately 46,000 units of RBCs per year, accrual was slower than anticipated, with nearly 9 months required before 80 patients completed the study protocol. The primary feasibility outcome was therefore not achieved. The principal cause was a smaller than anticipated number of RBC transfusions both meeting inclusion criteria and occurring during hours when research personnel were available. During the study period, a total of 29,662 RBCs were issued by the transfusion service. With the application of each inclusion criterion, the number of transfusions eligible diminished rapidly: 14,665 were issued to inpatients (not in the operating room); of these, 9,572 were issued to inpatients 65 years or older; of these, 7,645 were single RBC unit transfusions; and finally, of these, 3,052 were issued between Monday to Friday 8 am to 5 pm and were therefore available for screening of exclusion criteria by the research personnel. Because the enrollment period exceeded the anticipated 2-month period and due to limited resources, detailed documentation of reasons for exclusion was only performed from July 13 to November 3, 2016. For that period, amongst the 674 transfusions that met all inclusion criteria, 418 (62%) were excluded for severe renal impartment (145), prior enrollment in the study (98), hypokalemia (95), active bleeding (34), hyponatremia (25), planned same-day discharge (17), hemodynamical instability (2), and palliative patient status (2). An additional 177 (26%) eligible patients identified during this time could not be approached for consent: specific reasons included departmental exclusion (63), physician declined participation (41), transfusion started before patient approached (37), and prior request from patient not to be approached (36). The enrollment flow chart for the full study period is shown in Fig. 1.

The characteristics of the 80 patients who completed the study protocol are shown in Table 1. 47 (59%) patients were admitted for treatment or complications of malignancy, 43 (54%) patients had a history of cardiac disease (9% with a history of congestive heart failure), 24 (30%) had renal impairment and 26 (33%) were already receiving regular daily diuretics (predominantly furosemide) at time of trial enrollment. The RBC units transfused were all leukoreduced, had a mean storage duration of 3weeks at time of transfusion, with approximately one-half having been irradiated and none subject to plasma-volume reduction or washing. The majority of units were transfused over 2–4 hours (mean 167.7 minutes, SD +/− 46 minutes).

Feasibility outcomes are listed in Table 2. In addition to the primary feasibility outcome, several secondary feasibility outcomes did not meet pre-defined targets, including consent rate, receipt of treatment allocation, and completion of the follow-up protocol. A significant driver of the 20% consent rate, defined as the proportion of eligible patients who agreed to participate in the trial, was a request by the patient's attending physician that the patient not be approached; this was in fact requested as a departmental decision by the cardiac, lung, and stem cell transplant programs to not participate in the trial due to a desire to retain individual physician discretion in the management of pre-transfusion diuretic therapy. Seventy percent of patients (89 of 127) who were approached for the study consented to participate.

Post-transfusion vital signs performed within 4–8 hours of a completed transfusion, and post-transfusion laboratory tests performed within 12–30 hours of a completed transfusion, were only documented in 55% and 53% of cases, respectively, and post-transfusion labs drawn within 12–30 hours of transfusion were documented in only 51% of cases. The low compliance rate for these outcomes was due to missing documentation of the time the transfusion was completed. The poor compliance with documentation of fluid balance (44%), however, reflected the infrequency with which this assessment was actually performed.

The frequency of protocol deviations was similar between treatment arms (see Supplement for details). Notably, 21% of patients were ordered an additional blood product in the 24 hours following trial enrollment. Chest x-rays, which were left to physician discretion, were performed in only three of the five cases (60%) where increasing FiO2 requirements were documented post-transfusion.

Clinical outcomes are described in Table 3. The primary clinical outcome of TACO occurred in two (2.5%) patients, with one case observed in each study arm. The case occurring in the placebo arm occurred 212 minutes post-transfusion with the diagnosis made on the basis of pulmonary edema on chest x-ray, a ≥50% increase from baseline in serum BNP (with post-transfusion BNP above normal range), and evidence on physical exam of heart failure. The patient required 100% oxygen by non-rebreather mask but without need for mechanical ventilation; antibiotics were also prescribed. There were no long-term sequelae. The case was classified as grade two (severe). The TACO case occurring in the treatment arm manifested 258 minutes post-transfusion and was diagnosed on the basis of pulmonary edema on chest x-ray, a ≥50% increase from baseline in serum BNP (with post-transfusion BNP above normal range), and evidence of acute respiratory distress. The patient was managed with an increase in oxygen supplementation (from room air to 2 L by nasal prongs) without need for mechanical ventilation,

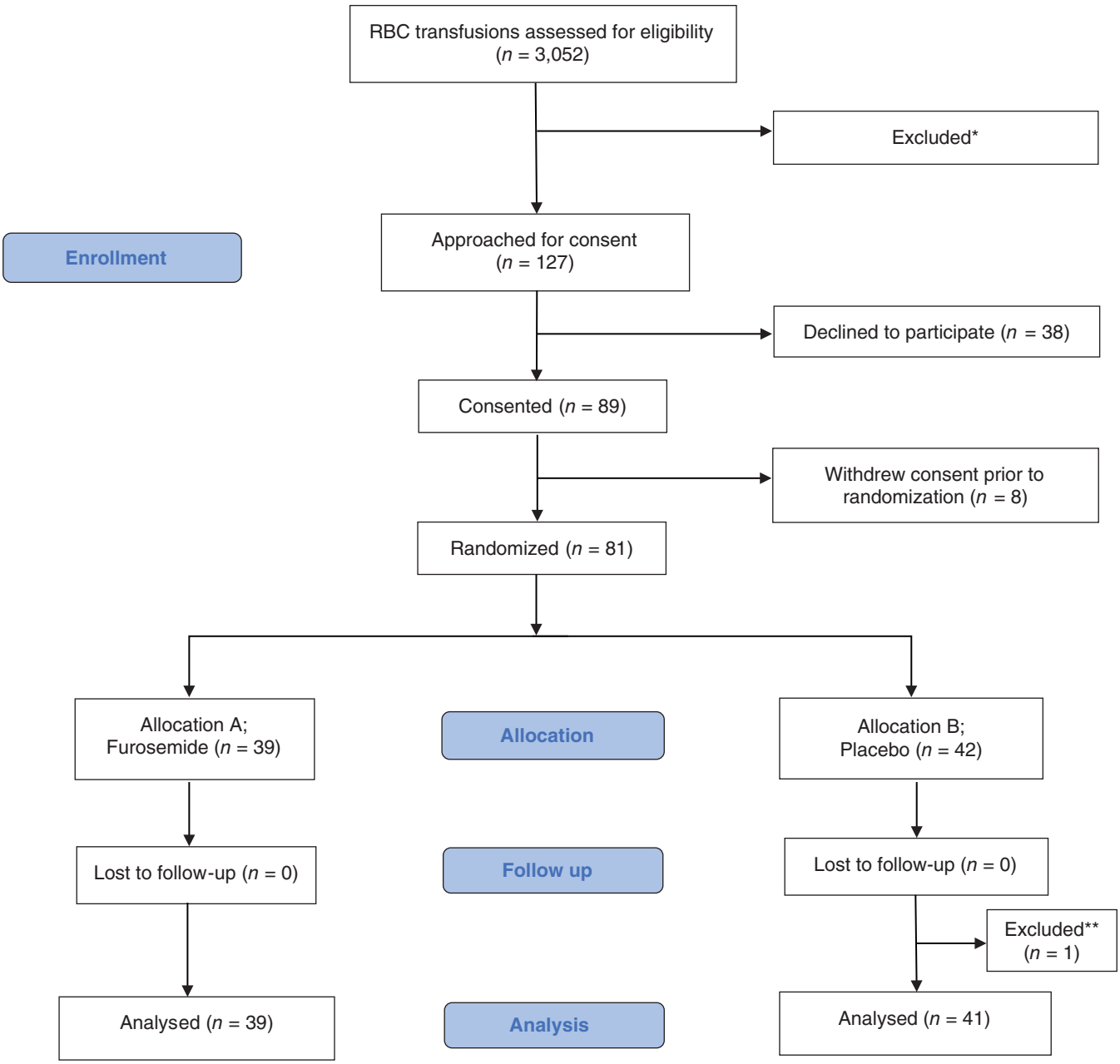

Fig. 1. Study Enrollment. *Reasons for exclusion collected from July 13 to November 3, 2016 (n = 418); an additional 177 eligible transfusions during this time could not be approached for consent. See text for details. **One patient excluded after randomization as was on inotropes and did not meet eligibility criteria. [Color figure can be viewed at wileyonlinelibrary.com]

and was given both bronchodilators and an additional dose of post-transfusion furosemide. This case was classified as grade one (non-severe).

As the primary focus of this study was to determine protocol feasibility, statistical comparisons of clinical outcomes were not performed. However, no clear difference was apparent between study arms in regard to the primary outcome (incidence of TACO), the surrogate marker of a post-transfusion systolic blood pressure increase ≥30 mmHg, or in any other secondary clinical outcome measure. Similarly, no toxicity from the dose of furosemide administered was apparent, as defined by the incidence of hypokalemia, hyponatremia, renal injury, hypotension, or other physician-reported harm.

DISCUSSION

This study represents the first adult randomized controlled clinical trial of diuretic therapy for the prevention of TACO. The overall incidence of TACO (2.5%, 95% CI 0.3–8.7%) confirmed

TABLE 1. Characteristics of Enrolled Patients

	Furosemide (N = 39)	Placebo (N = 41)	Total (N = 80)
Age (year, mean ± SD)	74.5 ± 7.6	74.7 ± 6.7	74.6 ± 7.1
Sex (N, %)			
Male	22 (55)	26 (63)	48 (60)
Female	17 (44)	15 (37)	32 (40)
Weight (kg, mean ± SD)	75.4 ± 16.6	74.6 ± 17.7	75.0 ± 17.0
BMI (mean ± SD)	27.7 ± 5.8	27.0 ± 5.5	27.3 ± 5.6
ECOG status (median, IQR)	2 (0–3)	2 (0–3)	2 (0–3)
Reason for admission (N, %)			
Cardiac or vascular surgery	3 (8)	2 (5)	5 (6)
Other surgery	3 (8)	4 (10)	7 (9)
Trauma/burn	1 (3)	1 (2)	2 (3)
Infection/sepsis	1 (3)	2 (5)	3 (4)
GI hemorrhage	1 (3)	0 (0)	1 (1)
Malignancy for chemotherapy	17 (44)	18 (44)	35 (44)
Febrile neutropenia	1 (3)	3 (7)	4 (5)
Other complication of malignancy	3 (8)	5 (12)	8 (10)
Stroke/transient ischemic attack	0 (0)	1 (2)	1 (1)
Anemia	2 (5)	3 (7)	5 (6)
Other	7 (18)	2 (5)	9 (11)
Location of transfusion (N, %)			
Ward	33 (85)	32 (78)	65 (81)
ICU/CCU/High-intensity unit	6 (15)	9 (22)	15 (19)
Renal disease			
GFR (mean ± SD)	73.9 ± 26.5	77.7 ± 34.2	75.8 ± 30.6
GFR <60 (#)	11 (28)	13 (32)	24 (30)
Cardiac disease (N, %)			
Any cardiac disease	24 (62)	19 (46)	43 (54)
History of congestive heart failure	5 (13)	2 (5)	7 (9)
Documented LVEF <40%	1 (3)	1 (2)	2 (3)
Chronic liver disease (N, %)	2 (5)	2 (5)	4 (5)
IF YES: MELD score (mean ± SD)	23 ± 4.2	22 ± 2.1	22 ± 2.9
Chronic diuretic use (N, %)			
Loop diuretic	12 (31)	12 (29)	24 (30)
Non-loop diuretic	4 (10)	2 (5)	6 (8)
Either	14 (36)	12 (30)	26 (32)
Pre-transfusion 24-hr fluid balance (ml, mean ± SD)	692.9 ± 722.2	671.8 ± 1050.2	681.1 ± 897.4
Pre-transfusion Hgb (g/L, mean ± SD)	72.4 ± 4.7	70.1 ± 5.1	71.2 ± 5.0
Age of blood product (days, mean ± SD)	21.5 ± 7.2	20.9 ± 9.4	21.2 ± 5.0
Product modifications			
Irradiated (N, %)	20 (51)	23 (56)	43 (54)
Plasma-volume reduced (N, %)	0 (0)	0 (0)	0 (0)
Washed (N, %)	0 (0)	0 (0)	0 (0)
Infusion time (minutes, mean ± SD)	168.9 ± 44	166.5 ± 49	167.7 ± 46
Length of stay following randomization (days, mean ± SD)	17.6 ± 22	19.8 ± 32	18.7 ± 28

BMI = body mass index; CCU = coronary care unit; ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; ICU = intensive care unit; LVEF = left ventricular ejection fraction; MELD = model for end-stage liver disease; SD = standard deviation.

what has been estimated in previous observational studies and suggests that the efficacy of pre-transfusion furosemide in preventing TACO could theoretically be demonstrated in this population: assuming a baseline TACO incidence of 3%, a sample size of approximately 2,600 patients (1,300 per treatment arm) would allow for the detection of a 40% relative risk reduction or greater with 80% power and an alpha of 0.05. Ten sites each enrolling 20–25 patients per month would allow such a trial to be completed within 1 year. However, the current protocol did not demonstrate feasibility in achieving this goal, primarily due to the lower than expected number of RBC transfusion episodes available for screening. The decision to exclude patients ordered more than one unit of RBCs at a time was likely a significant contributor to this, but as the administration of two units to a stable, non-bleeding patient is generally considered to be inappropriate practice (due in part to the increased risk of TACO thereby incurred), we felt that including two-unit RBCs transfusions would have compromised the external validity of the study results.[16] A more appropriate means of broadening inclusion criteria in future studies would be to lower the age limit: a review of reported TACO cases at the two institutions in this study revealed that the incidence of TACO in patients aged 50 years and older is in fact very similar to that in patients aged 65 years and older, and including this age group in future trials would increase the number of eligible patients by approximately one third.[19] Reconsidering some of the exclusion criteria (which eliminated nearly half of patients meeting inclusion criteria) may also provide a small increment in enrollment

TABLE 2. Feasibility Outcomes

Criterion	Definition	Target	Outcome
Time to enroll 80 patients	Interval between opening of enrollment and completion of study protocol by 80 patients	2 months	9 months
Proportion of RBC orders screened meeting criteria*	(# meeting inclusion criteria) ÷ (# meeting all eligibility criteria)	≥10%	38%
Proportion of eligible patients consenting to participate*	(# in whom consent obtained) ÷ (# meeting eligibility criteria)	≥25%	20%
Proportion of consenting patients receiving the allocated treatment	(# allocated treatment) ÷ (# consenting to treatment)	≥90%	86%
Proportion of randomized patients completing study follow-up protocol	(# completing outcome measures) ÷ (# administered allocated treatment)		
	• Vital signs documented pre-transfusion	≥80%	95%
	• Vital signs documented post-transfusion	≥80%	88%
	• Vital signs documented 4–8 post-transfusion	≥80%	91%
	• All pre-transfusion laboratory tests performed	≥80%	99%
	• All post-transfusion laboratory tests performed	≥80%	95%
	• Post-transfusion labs within 12–30 hours of transfusion end	≥80%	51%
	• Post-transfusion fluid balance documented	≥80%	44%
Proportion of randomized patients for whom blinding was maintained	(# with allocation remaining blinded until data analysis complete) ÷ (# completing all outcome measures)	100%	100%

* Assessment performed for July 13 to November 3, 2016 only: of 674 transfusions meeting all inclusion criteria, 256 (38%) had no exclusion criteria. Of these 256 eligible patients, 51 (20%) consented to participate.

numbers. Specifically, the mid-trial decision to allow patients with mild hypokalemia (potassium 3.0–3.4 mmol/L) to participate when provided potassium supplementation accounted for approximately 20% of subsequently enrolled patients and did not result in episodes of hypokalemia: all patients with baseline potassium levels of 3.0–3.4 mmol/L had a post-treatment potassium level within normal range.

Overall, however, the most significant driver of slow enrollment were limitations within the study protocol itself. The discovery that approximately two-thirds of patients meeting the primary inclusion criteria were transfused outside of regular working hours was unexpected; presumably 30%–40% of these would have not have had any exclusion criteria (ie., the same proportion as in patients transfused during regular working hours) and would therefore have been eligible to participate. Closer analysis suggested that many of these off-hour transfusions were being ordered on weekends and, particularly in critical care units, during early morning hours. While it is possible that this practice is institution-specific, future studies should have the capacity to capture more of these missed transfusions as a strategy to boost enrollment. Extending study coordinator hours to capture these patients would therefore be a potential means of increasing enrollment numbers in future trials, as well as possibly broadening the clinical profile of the enrolled population, which in this study had a large proportion of patients with malignancies. However, as extending enrollment hours would also dramatically increase study expenses, a more cost-effective modification in study protocol might be to enroll otherwise eligible patients before a transfusion is ordered (e.g., in the setting of progressive anemia) and then work collaboratively with the treating physician to schedule any future non-urgent transfusion during regular working hours. This approach might also improve the rate of enrollment by extending the narrow window between the receipt of a transfusion order by the blood transfusion laboratory and the subsequent issue of the blood product. Approaching patients in advance of a transfusion order might also increase consent rate as, anecdotally, patient refusal to participate in the study appeared to be driven less by concern with risks posed by the intervention than by overall fatigue and therefore a disinclination to review the trial protocol in the short time interval before their transfusion was scheduled to start. Finally, pre-transfusion enrollment might allow for full discussion amongst all members of the patient's clinical team, thereby avoiding the conflicting viewpoints that largely drove the withdrawal of patients who had already consented to participate. Given that many inpatients are transfused on more than one occasion during their stay, the use of more innovative study designs such as cluster randomized controlled trials (ie., in which institutions rather than individuals are the unit of randomization) could be considered as another means of speeding enrollment, and possibly increasing the generalizability of results, although such an approach would introduce significant complexity to the statistical analysis of the results obtained.[20]

Another limitation in the study protocol was the reliance on non-study personnel to perform the majority of the clinical documentation. In several instances, the lack of a documented transfusion stopping time meant that protocol adherence could not be fully assessed (e.g., the time interval between the transfusion and subsequent patient assessment). Maintaining close collaboration between study personnel and patient caregivers, and providing stricter guidelines regarding patient assessment and documentation, will therefore be an important consideration in

TABLE 3. Clinical and Laboratory Outcomes

	Furosemide (N = 39)	Placebo (N = 41)	Total (N = 80)
Change in HR (beats per minute, median, IQR)			
Initial	−2.0 (−5, 2)	−1.0 (−7, 6)	−1.5 (−6, 3)
Final	0.5 (−6, 9)	−1.0 (−9, 7)	0.0 (−7,8)
Change in SBP (mmHg, median, IQR)			
Initial	10.0 (0, 21)	3 (−6, 11)	6.5 (−2, 16)
Final	4 (−7, 16)	3 (−6, 12)	4 (−7, 16)
Patients with SBP increase ≥30 mmhg (N, %)			
Initial	5 (13)	2 (5)	7 (9)
Final	4 (10)	2 (5)	6 (8)
Patients with SBP decrease ≥30 mmhg (N, %)			
Initial	0 (0)	0 (0)	0 (0)
Final	3 (8)	2 (5)	5 (6)
Change in DPB (mmHg, median, IQR)			
Initial	5 (1,13)	1 (−2,7)	3.5 (−1.5, 9)
Final	3.5 (−4, 8)	4 (3,7)	4 (−4, 7)
Change in RR* (resp/min, median, IQR)			
Initial	0 (0, 0)	0 (0, 0)	0 (0, 0)
Final	0 (0, 0)	0 (0, 0)	0 (0, 0)
Change in Temperature (°C, median, IQR)			
Initial	0.1 (−0.2, 0.4)	0.1 (−0.2, 0.3)	0.0 (−0.2, 0.3)
Final	−0.1 (−0.4, 0.5)	0.1 (−0.4, 0.3)	−0.1 (−0.4, 0.4)
Change in SpO2%* (median, IQR)			
Initial	0.0 (−2.0, 1.0)	0.0 (−1.0, 1.0)	0.0 (−1.0, 1.0)
Final	0.0 (−1.0, 1.0)	0.0 (−1.0, 1.0)	0.0 (−1.0, 1.0)
Post−transfusion fluid balance (mL, median, IQR)	−112 (−328, 745)	357 (−579, 676)	87 (−414, 695)
Pre−post change in fluid balance (mL, median, IQR)	−878 (−1487, −445)	−871 (−1904, 615)	−871 (−1556, 359)
Post−transfusion change in Hgb (g/L, median, IQR)	12.0 (8, 14)	10.0 (8, 14)	11.5 (8. 14)
BNP proportional increase (median, IQR)	0.9 (0.7, 1.1)	1.1 (0.9, 1.4)	1.0 (0.8, 1.2)
BNP proportional increase >1.5 (N, %)	6 (15)	6 (15)	12 (15)
Na change (mmol/L, median, IQR)	0 (−1, 1)	0 (−2, 1)	0 (−2, 1)
Patients with post−transfusion Na <130 mmol/L (N, %)	0 (0)	0 (0)	0 (0)
K change (median mmol/L, IQR)	−0.3 (−0.5, 0.0)	0.1 (−0.2, 0.2)	−0.1 (−0.4, 0.2)
Patients with post−transfusion K <3.0 mmol/L (N, %)	0	0	0
Cr change (median μmol/L ± SD)	1.0 (−5.0, 4.0)	−2.0 (−5.0, 1.0)	−1.0 (−5.0, 3.0)
Cr proportional increase (median, IQR)	1.0 (1.0, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)
Patients with proportional Cr incr >30% (N, %)	2 (5)	0 (0)	2 (3)
Transfusion reaction (N, %)	1 (3)	1 (2)	2 (3)
TACO definition met (N, %)	1 (3)	1 (2)	2 (3)
Complications at 24 hours (N, %)			
Increased oxygen requirements	6 (15)	6 (15)	12 (15)
Arrhythmia	0 (0)	0 (0)	0 (0)
Inotropes	0 (0)	0 (0)	0 (0)
Mechanical ventilation	1 (3)	2 (5)	3 (4)
Complications at 7 days (N, %)			
Increased oxygen requirements	6 (15)	13 (32)	19 (24)
Arrhythmia	0 (0)	0 (0)	0 (0)
Acute coronary syndrome	0 (0)	0 (0)	0 (0)
Mechanical ventilation	0 (0)	0 (0)	0 (0)
Admission to intensive care	1	1	2
Death by 30 days (N, %)	2 (5)	7 (17)	9 (11)
Death during hospital stay (N, %)	2 (5)	11 (27)	13 (16)
Time from randomization to discharge (days, median, IQR)	8 (3, 22)	7 (4, 17)	7.0 (4, 22)
Time from randomization to death (days, median, IQR)	14.5 (1, 28)	17 (7, 46)	17.0 (7, 43)

* limited to patients with SpO2 measured at same FiO2.vvv.
Initial refers to change from baseline to 6 hours post transfusion.
Final refers to change from baseline to 12−30 hours post transfusion.
BNP = brain natriuretic peptide; Cr = creatinine; DBP = diastolic blood pressure; HR = heart rate; IQR = interquartile range; K = potassium; Na = sodium; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation; SpO2 = oxygen saturation; TACO = transfusion-associated circulatory overload.

the success of any future trials. Mandating pre- and post-transfusion weight measurement may also prove to be a more reliable measurement of diuretic effect than tracking urine output, which was generally performed poorly in the current study.

Uncertainty regarding the optimal dose of furosemide to prevent circulatory overload is a further limitation of the study design. The choice of 20 mg, administered intravenously, was derived inferentially from available pharmacokinetic studies, clinical trials of this medication in other settings, and local practice audits.[2,21] In healthy subjects, a furosemide dose of 40 mg will prompt a maximal diuresis of 3–4 liters,[22] which would have greatly exceeded the fluid challenge represented

by a single unit of RBCs (approximately 300 mL).[23] However, diuretic responsiveness may be blunted in patients with medical comorbidities.[12,24] In randomized controlled trials of furosemide for the treatment of acute decompensated congestive heart failure, for example, weight loss averaged only 400 g for every 40 mg of intravenous furosemide administered,[25,26] reflecting the relative diuretic resistance in this population. Future trials are therefore needed to determine the most appropriate dose of prophylactic pre-transfusion furosemide. The reason for the lack of any apparent difference in any predefined clinical outcome between the furosemide and placebo arms can only be speculated upon given that the study was underpowered to detect such a difference. One possible explanation, however, is a deficiency in the follow-up protocol employed. A recently published study by our group, for example, has shown that NT-pro-BNP may have superior test characteristics to BNP in detecting circulatory strain in transfused inpatients.[27] In addition, the poor documentation of patient fluid balance and inconsistent ordering of chest imaging in response to increased oxygen requirements in the present trial may indicate that some subtle cases of TACO were missed. Indeed, the very explicit criteria used in this study for diagnosing TACO, utilized for the purpose of minimizing subjectivity and bias, is also a potential limitation, given that the defining criteria for TACO are continuously evolving.

In summary, a pilot randomized controlled trial of pre-transfusion furosemide for the prevention of circulatory overload revealed that changes to the protocol will be required and will need to be reassessed for feasibility in another pilot trial before proceeding to a large-scale, adequately powered study. Opportunities to increase enrollment, improve outcome documentation, and intensify treatment effect have been identified and will inform the design of future feasibility trials.

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CONFLICTS OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

1. Andrzejewski C Jr, Casey MA, Popovsky MA. How we view and approach transfusion-associated circulatory overload: pathogenesis, diagnosis, management, mitigation, and prevention. Transfusion 2013;53:3037-47.
2. Lieberman L, Maskens C, Cserti-Gazdewich C, et al. A retrospective review of patient factors, transfusion practices, and outcomes in patients with transfusion-associated circulatory overload. Transfus Med Rev 2013;27:206-12.
3. Clifford L, Jia Q, Yadav H, et al. Characterizing the epidemiology of perioperative transfusion-associated circulatory overload. Anesthesiology 2015;122:21-8.
4. Rana R, Fernández-Pérez ER, Khan SA, et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. Transfusion 2006;46:1478-83.
5. Fatalities reported to FDA following blood collection and transfusion: annual summary for fiscal year 2015 [Internet]. U.S. Food and Drug Administration; 2016. Available from: https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM598243.pdf
6. Health Canada Transfusion Transmitted Injuries Surveillance System, 2006–2012 Report. [Internet]. Public Health Agency of Canada; 2014. Available from: http://www.phac-aspc.gc.ca/hcai-iamss/ttiss-ssit/index-eng.php
7. Bolton-Maggs PH. Conference report: the 2015 SHOT symposium and report–what's new? Transfus Med 2015;25:295-8.
8. Alam A, Lin Y, Lima A, et al. The prevention of transfusion-associated circulatory overload. Transfus Med Rev 2013;27:105-12.
9. Balegar VKK, Kluckow M. Furosemide for packed red cell transfusion in preterm infants: a randomized controlled trial. J Pediatr 2011;159:913-8.
10. Sarai M, Tejani AM. Loop diuretics for patients receiving blood transfusions. Cochrane Database of Syst Rev. 2015;(2):CD010138. https://doi.org/10.1002/14651858.CD010138.pub2.
11. Regan DM, Markowitz MA. AABB Association Bulletin #15-02: Transfusion Associated Circulatory Overload. AABB. 2015. Available from: http://www.aabb.org/programs/publications/bulletins/Docs/ab15-02.pdf.
12. ter Maaten JM, Dunning AM, Valente MA, et al. Diuretic response in acute heart failure—an analysis from ASCEND-HF. Am Heart J 2015;170:313-21.
13. Jhund PS, McMurray JJ, Davie AP. The acute vascular effects of frusemide in heart failure. Br J Clin Pharmacol 2000;50:9-13.
14. Nand N, Gupta SP, Gupta MS. Hemodynamic evaluation of blood transfusion in chronic severe anemia with special reference to speed of transfusion. Jpn Heart J 1985;26:759-65.
15. Tseng E, Spradbrow J, Cao X, et al. An order set and checklist improve physician transfusion ordering practices to mitigate the risk of transfusion-associated circulatory overload. Transfus Med 2016;26:104-10.
16. Choosing Wisely Canada. Transfusion Medicine. Canadian Medical Association; 2017. https://choosingwiselycanada.org/transfusion-medicine/.
17. The National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol (vers. 2.5). Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention; 2018. https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf.
18. National Institutes of Health, National Cancer Institute. Common terminology for adverse events (vers. 5.0). United States

Department of Health and Human Services; 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
19. Cserti-Gazdewich CM, Callum J, Lin Y, et al. Identifying the target age for trials to test strategies to decrease the incidence of transfusion-associated circulatory overload (TACO). Transfusion 2016;56:166A.
20. Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. Am J Public Health 2004;94:416-22.
21. Lin Y, Cohen R, Armali C, et al. Transfusion-associated circulatory overload prevention: a retrospective observational study of diuretic use. Vox Sang 2018;113:386-92.
22. Brater DC. Update in diuretic therapy: clinical pharmacology. Semin Nephrol 2011;31:483-94.
23. Circular of information for the use of blood components: red blood cells leukoreduced (LR). Canadian Blood Services. 2014. Available from: https://www.blood.ca/sites/default/files/RedBloodCellsLeukocytes.pdf.
24. Oh SW, Han SY. Loop diuretics in clinical practice. Electrolyte Blood Press 2015;13:17-21.
25. Valente MA, Voors AA, Damman K, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J 2014;35:1284-93.
26. Voors AA, Davison BA, Teerlink JR, et al. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF. Eur J Heart Fail 2014;16:1230-40.
27. Callum J, Cressman A, Cohen R, et al. Cardiac stress biomarkers after red cell transfusion in patients at risk for transfusion associated circulatory overload: a prospective observational study. Transfusion 2018;58:2139-48.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. Supporting information.