

A systematic review and meta-analysis on the effect of goal-directed fluid therapy on postoperative outcomes in renal transplantation surgeries

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ABSTRACT

Introduction: This systematic review and meta-analysis investigated the impact of intraoperative goal-directed therapy (GDT) compared with conventional fluid therapy on postoperative outcomes in renal transplantation recipients, addressing this gap in current literature.

Method: A systematic search of patients aged ≥ 18 years who have undergone single-organ primary renal transplantations up to June 2022 in PubMed, Embase, Scopus and CINAHL Plus was performed. Primary outcome examined was postoperative renal function. Secondary outcomes assessed were mean arterial pressure at graft reperfusion, intraoperative fluid volume and other postoperative complications. Heterogeneity was tested using I^2 test. The study protocol was registered on PROSPERO.

Results: A total of 2459 studies were identified. Seven eligible studies on 607 patients were included. Subgroup assessments revealed potential renal protective benefits of GDT, with patients receiving cadaveric grafts showing lower serum creatinine on postoperative days 1 and 3, and patients monitored with arterial waveform analysis devices experiencing lower incidences of postoperative haemodialysis. Overall analysis found GDT resulted in lower incidence of tissue oedema (risk ratio [RR] 0.34, 95% CI 0.15–0.78, $P=0.01$) and respiratory complications (RR 0.39, 95% CI 0.17–0.90, $P=0.03$). However, quality of data was deemed low given inclusion of non-randomised studies, presence of heterogeneities and inconsistencies in defining outcomes measures.

Conclusion: While no definitive conclusions can be ascertained given current limitations, this review highlights potential benefits of using GDT in renal transplantation recipients. It prompts the need for further standardised studies to address limitations discussed in this review.

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Keywords: end-stage renal failure, goal-directed therapy, postoperative outcomes, renal transplantation, systematic review

CLINICAL IMPACT

What is New

- Goal-directed therapy (GDT) in renal transplantation surgeries may offer benefits in postoperative outcomes, including reduced incidence of tissue oedema and respiratory complications.
- GDT showed potential renal protective benefits, with lower early postoperative serum creatinine levels in cadaveric transplantations, and lowered postoperative haemodialysis incidences in patients monitored with arterial waveform analysis devices.

Clinical Implications

- This underscores the importance of considering fluid management strategies in renal transplantation surgeries.
- GDT's impact varies across patient groups and modalities, emphasising the necessity for tailored approaches.

INTRODUCTION

Renal transplantation is the superior treatment for chronic kidney disease patients, providing better survival outcomes and quality of life compared with other renal replacement therapies.¹ The recipient's intraoperative fluid management is crucial due to its impact on postoperative graft function, morbidity and mortality.²⁻⁶ However, fluid management in such patients is challenging due to their impaired ability to maintain fluid balance, which increases the risk of complications such as fluid overload or depleted intravascular volume, leading to graft dysfunction post-transplantation.

The main intraoperative objective for renal transplantation recipients is to ensure sufficient

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graft perfusion. Traditionally, this is achieved through aggressive intraoperative volume expansion. Conventional methods involve maintaining targets for heart rate, blood pressure, central venous pressure (CVP) or urine output.^{7,8} However, studies have demonstrated that these conventional fluid therapy protocols inaccurately assess fluid responsiveness and can lead to complications related to excessive fluid administration.⁹⁻¹³

Goal-directed therapy (GDT) is a protocol that optimises flow-related parameters like cardiac index, stroke volume index, stroke volume variation, stroke volume and pulse pressure variation. GDT dynamically monitors a patient's fluid responsiveness per the Frank-Starling curve. It individualises the amount and timing of fluid administration to avoid under- or over- resuscitation. GDT includes a spectrum of techniques like (1) transoesophageal echocardiogram, (2) pulmonary artery catheterisation, (3) arterial waveform analysis-based techniques (e.g. FloTrac and ClearSight, Edwards Lifesciences, Irvine, CA, US), (4) oesophageal Doppler monitoring and (5) bio-impedance-based technologies.¹⁴

Several studies have acknowledged potential benefits of GDT, including improved renal perfusion and mortality benefits.^{15,16} However, benefits vary based on surgical settings.¹⁷ Therefore, there is interest in studying the use of GDT in renal transplantation recipients due to the complexity of fluid management. It is crucial for practitioners to ensure adequate preload for end-organ tissue perfusion while avoiding complications related to aggressive fluid administration.^{18,19}

However, current limited literature comparing GDT and conventional therapy in the context of renal transplantation has yielded mixed results, and ideal clinical goals for GDT remain uncertain.²⁰ This prompted our team to conduct a systematic review and meta-analysis to ascertain postoperative benefits of GDT protocols compared with conventional fluid therapy protocols.

METHOD

This review was prospectively registered and conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. The study protocol was registered in the international prospective register of systematic reviews.²¹ Institutional review board approval was not required for this secondary analysis of previously published data.

The search strategy was formulated using the Population, Intervention, Control, Outcome and Study model, a recommended approach for systematic reviews designed to study clinical

interventions. The primary selection criteria of our review are shown in Supplementary Table S1. Articles were regarded as potentially eligible if they met all criteria.

Population

Only adult end-stage renal failure patients aged ≥ 18 years, who have undergone their first single-organ renal transplantation were included. Paediatric patients and patients who have undergone multiple organ transplantation operations or secondary renal transplantation were excluded.

Intervention

The intervention group had to utilise goal-directed therapy, defined as intraoperative use of cardiac output monitoring and the manipulation of dynamic flow-related parameters using fluids alone or in combination with inotropes or vasopressors.

Control

The control group had to receive conventional fluid therapy, defined as the routine administration of fluids and/or inotropic drugs based on either a standard institutional-based fluid protocol or targeting non-flow-related haemodynamic parameters using fluids alone or in combination with inotropes or vasopressors.

Outcomes

The primary outcome examined in the eligible studies was postoperative renal function, encompassing all markers of renal function. Secondary outcomes assessed included mean arterial pressure at reperfusion, volume of intraoperative intravenous fluids administered, and the incidence of any non-renal postoperative complications. No limitations were imposed on the type of postoperative complications considered.

Study design

Only interventional studies were included with no restrictions imposed on setting, publication date or ethnic group. Only articles published in English were considered.

A systematic search for relevant articles was performed in PubMed, EMBASE, Scopus and CINAHL Plus from inception until June 2022. A logical construction of search strings, comprising both medical subject headings terms and free-text search terms, was created specific to each database as shown in Supplementary Table S2. Reference sections of all eligible studies were also searched for possible inclusion of additional studies.

Two independent reviewers screened the full-text articles that were retrieved. In case of disagreements in the choice of articles, a third and fourth

reviewer were consulted to reach a final consensus. The shortlisted full-text articles were approved by all the authors prior to the data extraction process. A data extraction table was used to include relevant preoperative information of the renal transplantation recipients, types of donor kidney, modality of fluid status optimisation and postoperative outcomes measured.

The risk of bias was assessed using the Cochrane Collaboration risk of bias tool, which considers selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. All outcomes were also assessed for publication bias with Egger's regression test, and a funnel plot was constructed and inspected for asymmetry.

Data analysis was performed using Review Manager (RevMan) [Computer Program], Version 5.4, The Cochrane Collaboration, 2020. Continuous data were presented as mean difference (MD) and its 95% confidence interval (CI). Dichotomous data were presented as risk ratio (RR) and 95% CI. The individual effect sizes were weighted per the reciprocal of their variance. If the standard deviation was not available for continuous outcomes, it was calculated as per the Cochrane Collaboration guidelines. Heterogeneity was examined using the I^2 test.

In determining the choice of statistical methods, the random effects model was chosen as the default model due to the intrinsic heterogeneity of the research question with expected sources from differences in immunotherapy regimens and recipient as well as donor graft characteristics. However, for outcomes with a minimal possibility of heterogeneity (i.e. I^2 test equating to zero), the fixed-effects model was employed. This decision was made to counteract the potential result inflation that could arise in random effects models when dealing with small studies.²²

The meta-analysis results were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for certainty. The initial quality of evidence was considered moderate when a mix of randomised and non-randomised studies was included, and low when all studies were non-randomised. Further downgrading occurred if the I^2 value exceeded 40% or its P value was <0.1 , indicating significant heterogeneity. Downgrading also took place in case of inconsistencies among studies (e.g. contradictory results or outcome definition variations) or when there was notable imprecision. No downgrading was necessary due to publication biases.²³

Subgroup analyses were conducted based on the type of donor kidney received (living versus

cadaveric), the modality of GDT (arterial waveform analysis technique versus oesophageal monitoring technique), and the methods of fluid optimisation (fluids alone versus fluids combined with inotropes and/or vasopressors) due to their influence on postoperative graft function. Chi-squared tests for heterogeneity were utilised to identify the distinctions between subgroups.

RESULTS

The study selection process is shown in Supplementary Fig. S1. There were 2459 unique publications identified from the databases; 2446 were excluded after screening through titles and abstracts. Full texts of the remaining 13 articles with titles and abstracts that met the inclusion criteria were retrieved. Thereafter, 6 articles were excluded as they either did not measure any postoperative renal outcomes, were non-interventional studies, included paediatric patients, or involved secondary renal transplantation or multi-organ transplantation surgery. The reference list of retrieved studies was screened through, but did not identify any additional articles. Seven articles were eventually included in the study.²⁴⁻³⁰

Table 1 presents the characteristics of the included studies, which were published between 2015 and 2022. The sample sizes ranged from 39 to 214 participants. Various fluid monitoring techniques were employed in both the GDT and conventional therapy groups. One study (Cassai et al.)²⁴ compared arterial waveform analysis technique to free fluid administration. Four studies (Cavaleri et al., Goyal et al., Kannan et al. and Zhang et al.)^{25,27,28,30} compared arterial waveform analysis technique to maintaining CVP targets, either alone or in combination with systolic blood pressure and mean arterial pressure (MAP) targets. Two studies (Corbella et al. and Srivastava et al.)^{26,29} compared oesophageal Doppler monitoring to maintaining CVP targets with or without a combination of systolic blood pressure and MAP targets. The type of donor kidney varied among the studies. Two studies (Goyal et al. and Srivastava et al.) received grafts from living donors. Two studies (Cassai et al. and Corbella et al.) received cadaveric grafts. Three studies (Cavaleri et al., Kannan et al. and Zhang et al.) did not specify the type of graft or included both living and cadaveric grafts in their patient selection. Furthermore, 3 studies (Cassai et al., Goyal et al. and Srivastava et al.) optimised targets using fluid therapy alone, while 4 studies (Cavaleri et al., Corbella et al., Kannan et al. and Zhang et al.) utilised a combination of fluid therapy and inotropes and/or vasopressors.

Table 1. Summary of characteristics and main outcomes of included studies.

Author (year)	RCT	Country	Type of donor kidney	GDT (n)	Control (n)	GDT protocol	Control protocol	Therapy method	Measure of postoperative renal function	Postoperative renal outcome	Intraoperative intravenous fluid	MAP at reperfusion	Other postoperative outcomes	Conclusion
Cassai et al. (2020) ²⁴	Yes	Italy	Cadaveric	19	20	Arterial waveform analysis: PPV <12%	Baseline 10 mL kg ⁻¹ h ⁻¹ infusion with one for one replacement for bleeding	Fluids	Dialysis within 1 week of transplant; serum biomarkers (urea, creatinine), urine output	GDT significantly reduced serum urea and creatinine levels. No statistical difference was found in urine output and incidence of dialysis.	GDT group used significantly less fluids.	Both groups were comparable.	No difference in incidences of patients with clinical and radiological signs of fluid overload requiring oxygen therapy, cumulative furosemide dose or total length of stay.	GDT is as adequate a strategy as liberal fluid management and may reduce incidences of fluid overload.
Cavaleri et al. (2019) ²⁵	No	Italy	Unknown	33	33	Arterial waveform analysis: SVI <10% of optimal SV	CVP 8–12 mmHg MAP ≥80 mmHg	Fluids and vasoactive agents	Dialysis within 1 week of transplant; serum biomarkers (creatinine, blood urea nitrogen, potassium); urine output	GDT significantly reduced serum creatinine level and incidence of dialysis. No statistical difference in serum biomarkers or urine output.	GDT group used less fluids but not statistically significant.	Both groups were comparable.	GDT group had statistically fewer acute coronary syndromes in first postoperative week, lower rate of ileus in first 72h post-transplant. No difference in respiratory distress syndrome, pneumonia, acute pulmonary oedema, congestive cardiac failure or 30-day morbidity.	GDT may be renal protective and may reduce postoperative morbidity.

Table 1. Summary of characteristics and main outcomes of included studies. (Cont'd)

Author (year)	RCT	Country	Type of donor kidney	GDT (n)	Control (n)	GDT protocol	Control protocol	Therapy method	Measure of postoperative renal function	Postoperative renal outcome	Intraoperative intravenous fluid	MAP at reperfusion	Other postoperative outcomes	Conclusion
Corbella et al. (2018)²⁶	Yes	Canada	Cadaveric	26	24	Oesophageal Doppler monitoring: SV >75% baseline	CVP 12–15 mmHg Systolic blood pressure >100 mmHg	Fluids and inotropes	Dialysis within 1 week of transplant; serum biomarkers (creatinine)	No difference between groups in all measures.	GDT group used more fluids but not statistically significant.	Not mentioned.	GDT group had statistically more incidences of cardiac events that included new onset arrhythmia, myocardial infarction, pulmonary embolism, cardiogenic pulmonary oedema and cardiac arrest.	Further trials are required to determine the benefits of GDT.
Goyal et al. (2022)²⁷	Yes	India	Living	35	40	Arterial waveform analysis: PPV <10–13%	CVP >15 mmHg	Fluids	Dialysis within 1 week of transplant; serum biomarkers (creatinine), urine output	No difference between groups in all measures.	GDT group used less fluids but not statistically significant.	Both groups were comparable.	GDT group had statistically less incidences of tissue oedema (swelling on eyelid, face and feet). No difference in incidences of mechanical ventilation, postoperative nausea and vomiting, pulmonary oedema and postoperative serum lactate levels.	GDT may be renal protective and may reduce postoperative morbidity.

Table 1. Summary of characteristics and main outcomes of included studies. (Cont'd)

Author (year)	RCT	Country	Type of donor kidney	GDT (n)	Control (n)	GDT protocol	Control protocol	Therapy method	Measure of postoperative renal function	Postoperative renal outcome	Intraoperative intravenous fluid	MAP at reperfusion	Other postoperative outcomes	Conclusion
Kannan et al. (2022)²⁸	Yes	India	Mixed	35	35	Arterial waveform analysis; PPV <9%	CVP 5 mmHg until the clamping of donor renal vessels; CVP 12–15 mmHg at reperfusion	Fluids and vasoactive agents	Dialysis within 1 week of transplant; serum biomarkers (urea, creatinine, rate of creatinine reduction); urine output	No difference between groups in all measures.	GDT group used significantly less fluids.	Both groups were comparable.	No difference in serum lactate levels; and no difference in tissue oedema or need for mechanical ventilation between the groups.	GDT reduces total intraoperative fluids used but further studies are required to determine benefits of postoperative morbidity.
Srivastava et al. (2015)²⁹	No	India	Living	110	104	Oesophageal Doppler monitoring; flow time corrected >350 ms	CVP >15 mmHg	Fluids	Dialysis within 1 week of transplant; serum biomarkers (creatinine); urine output	No difference between groups in all measures.	GDT group used significantly less fluids.	Both groups were comparable.	GDT group had statistically less need for postoperative supplemental oxygen, and incidence of postoperative visual oedema. No difference in postoperative mechanical ventilation.	GDT may be beneficial in reducing fluid overload complications.
Zhang et al. (2021)³⁰	No	China	Unknown	49	48	Arterial waveform analysis; SVV <10%	CVP 6–9 mmHg MAP $\pm$ 20% of basal value and >90 mmHg	Fluids and vasoactive agents	Dialysis within 1 week of transplant; serum biomarkers (creatinine, blood urea nitrogen, creatinine clearance rate); urine output	GDT group had significantly lower serum creatinine level and incidence of dialysis but no statistical difference in serum biomarkers or urine output.	GDT group used significantly less fluids.	Both groups were comparable.	No difference in pulmonary oedema, respiratory failure or heart failure.	GDT can reduce intraoperative fluid infusion, and has benefits in postoperative renal outcomes.

CVP: central venous pressure; GDT: goal-directed therapy; MAP: mean arterial pressure; PPV: pulse pressure variation; RCT: randomised controlled trial; SV: stroke volume; SVI: stroke volume index; SW: stroke volume variation
 Superscript numbers: refer to REFERENCES

Included studies had at least 1 potential source of bias (Supplementary Table S3). Three of 7 studies (Cassai et al., Corbella et al. and Kannan et al.) had appropriate methods of randomisation with concealed allocation. However, blinding of the outcome assessors was unclear in all studies. Lack of standardisation of primary outcomes and measures of outcomes across all studies led to risk of detection bias and confounding. Risk of detection bias was further increased with the use

of subjective measures such as visual assessment of tissue oedema. No significant intercepts were found in the Egger's regressions, and there were no outlier studies identified upon visual inspection of the funnel plots, indicating no publication bias.

The results of the meta-analyses and the GRADE ratings are shown in Table 2. Forest plots of incidences of postoperative haemodialysis, tissue oedema and respiratory complications are shown in Fig. 1.

Table 2. Effect of intraoperative fluid protocols on postoperative outcomes in adult renal transplantation recipients. Summary of the meta-analyses with GRADE rating of evidence.

Outcome variable	No. of studies	No. of subjects		MD or RR (95% CI)	P value	I ² ^b (P value)	Random or fixed effects	Quality of evidence (GRADE)
		GDT	Control ^a					
Postoperative haemodialysis	7	308	303	RR = 0.64 (0.33 to 1.24)	0.19	52% (P = 0.06)	Random	Low
POD 0 urine output, L	3	194	187	MD = -0.05 (-0.30 to 0.19)	0.66	0% (P = 0.93)	Fixed	Moderate
POD 1 urine output, L	5	247	240	MD = 0.03 (-0.32 to 0.37)	0.88	36% (P = 0.18)	Random	Moderate
POD 3 urine output, L	3	192	185	MD = 0.15 (-0.28 to 0.58)	0.50	78% (P = 0.01)	Random	Very Low
POD 7 urine output, L	2	143	137	MD = 0.39 (-0.18 to 0.96)	0.18	69% (P = 0.08)	Random	Very Low
POD 0 serum creatinine, mg.dL ⁻¹	6	275	271	MD = -0.29 (-0.67 to 0.09)	0.13	0% (P = 0.85)	Fixed	Moderate
POD 1 serum creatinine, mg.dL ⁻¹	7	308	304	MD = -0.27 (-0.91 to 0.38)	0.42	72% (P = 0.002)	Random	Low
POD 3 serum creatinine, mg.dL ⁻¹	6	273	269	MD = -0.28 (-0.88 to 0.32)	0.37	58% (P = 0.04)	Random	Low
POD 7 serum creatinine, mg.dL ⁻¹	6	273	269	MD = -0.38 (-0.85 to 0.09)	0.11	49% (P = 0.08)	Random	Low
POD 0 serum urea, mmol.L ⁻¹	2	84	83	MD = -1.29 (-3.83 to 1.26)	0.32	0% (P = 0.39)	Fixed	Moderate
POD 1 serum urea, mmol.L ⁻¹	4	137	136	MD = -1.01 (-3.26 to 1.23)	0.38	0% (P = 0.61)	Fixed	Moderate
POD 3 serum urea, mmol.L ⁻¹	3	102	101	MD = -1.95 (-6.12 to 2.21)	0.36	44% (P = 0.17)	Random	Low
POD 7 serum urea, mmol.L ⁻¹	2	53	53	MD = -2.55 (-12.43 to 7.34)	0.61	68% (P = 0.08)	Random	Low
Tissue oedema ^c	4	199	199	RR = 0.31 (0.12 to 0.79)	0.01	0% (P = 0.90)	Fixed	Low
Respiratory complications ^d	7	308	303	RR = 0.39 (0.17 to 0.90)	0.03	0% (P = 0.67)	Fixed	Low
Cardiovascular complications ^e	2	59	57	RR = 1.03 (0.02 to 49.30)	0.99	86% (P = 0.007)	Random	Very Low
Serum lactate, mmol.L ⁻¹	2	70	75	MD = 4.90 (-5.30 to 15.10)	0.35	100% (P < 0.00001)	Random	Low
Length of stay, days	3	94	92	MD = -0.14 (-0.34 to 0.06)	0.17	0% (P = 0.99)	Fixed	Low

Table 2. Effect of intraoperative fluid protocols on postoperative outcomes in adult renal transplantation recipients. Summary of the meta-analyses with GRADE rating of evidence. (Cont'd)

Outcome variable	No. of studies	No. of subjects		MD or RR (95% CI)	P value	I ² ^b (P value)	Random or fixed effects	Quality of evidence (GRADE)
		GDT	Control ^a					
Intraoperative MAP at reperfusion, mmHg	6	248	242	MD = -0.33 (-1.8 to 1.17)	0.67	32% (P = 0.20)	Random	Low

CI: confidence interval; GDT: goal-directed therapy; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MAP: mean arterial pressure; MD: mean difference; POD: postoperative day; RR: risk ratio

^a Routine administration of fluids and/or inotropic drugs based on either a standard institutional-based fluid protocol or targeting non-flow-related haemodynamic parameters.

^b Heterogeneity coefficient >40% was considered significant.

^c Clinical and/or radiological signs of excessive fluid accumulation.

^d Need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure.

^e New-onset arrhythmia, myocardial infarction, pulmonary embolism, cardiogenic pulmonary oedema or cardiac arrest.

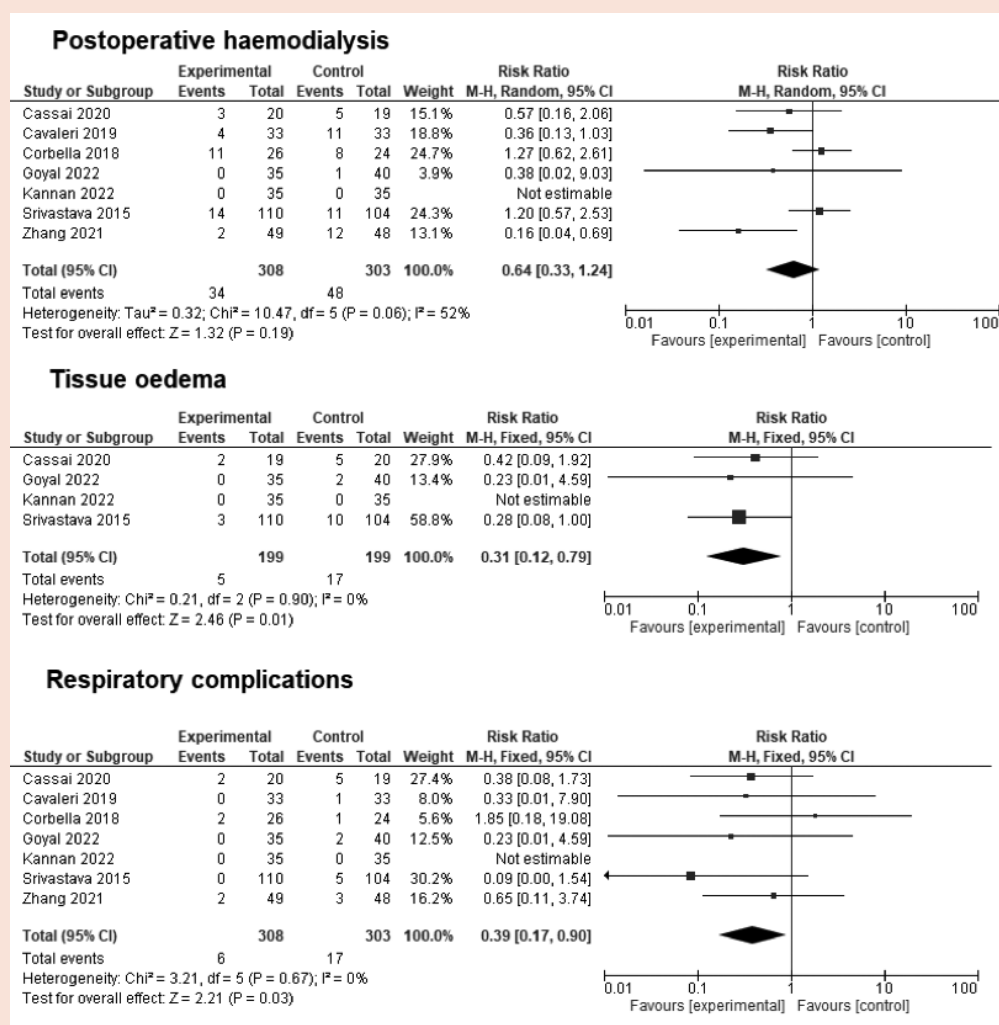
Population: adult (age ≥18 years) end-stage renal failure patients undergoing first single-organ renal transplantation surgery.

Intervention: GDT protocols.

Control: conventional fluid therapy protocols.

Values in bold are statistically significant.

Fig. 1. Forest plots of meta-analyses performed for incidences of postoperative haemodialysis, tissue oedema and respiratory complications. No statistical difference in overall incidences of postoperative haemodialysis (risk ratio [RR] 0.64, 95% confidence interval [CI] 0.33–1.24, $P=0.19$). However, lower incidences of postoperative tissue oedema and respiratory complications were found in the GDT group (RR 0.31, 95% CI 0.12–0.79, $P=0.01$ and RR 0.39, 95% CI 0.17–0.90, $P=0.03$, respectively).



M-H: Mantel-Haenszel test

The overall data analysis indicated no statistically significant difference in the primary outcome of postoperative renal indices. Incidence of postoperative haemodialysis within the first week of transplantation was reported in all 7 studies. There was no statistical difference between GDT versus conventional protocols ($P=0.19$). Other postoperative renal markers, such as urine output, serum creatinine and serum urea, also showed no significant difference in the first 7 postoperative days (all $P>0.05$).

Four studies (Cassai et al., Goyal et al., Kannan et al. and Srivastava et al.) measured incidences of postoperative tissue oedema, defined as clinical and/or radiological signs of excessive fluid accumulation. The likelihood of postoperative tissue oedema was significantly lower in the GDT group compared with the conventional group (RR 0.31, 95% CI 0.12–0.79, $P=0.01$). All 7 studies reported respiratory complications, which included the need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure. Patients in the GDT group were less likely to have respiratory complications than their counterparts in the conventional group (RR 0.39, 95% CI 0.1–0.90, $P=0.03$).

In all 7 studies, the total amount of intraoperative fluids used was reported, and no statistically significant difference was found between GDT and conventional protocols ($P=0.25$). Six studies reported intraoperative MAP at reperfusion.^{24,25,27,28-30} There was no statistical difference between GDT versus conventional protocols ($P=0.67$).

Other secondary outcomes that were described in the original studies also yielded insignificant results. Two studies (Cavaleri et al. and Corbella et al.) analysed incidences of cardiovascular complications, which included new onset arrhythmia, myocardial infarction, pulmonary embolism, cardiogenic pulmonary oedema, or cardiac arrest. Pooled estimates of these found no difference in such cardiovascular complications ($P=0.99$). Two studies (Kannan et al. and Goyal et al.) analysed postoperative serum lactate and found no statistical difference between groups ($P=0.35$). Three studies (Cassai et al., Corbella et al. and Zhang et al.) compared length of stay between intervention and control groups, and found no statistical difference as well ($P=0.17$).

Subgroup analyses were conducted to compare outcomes between patients who received kidney grafts from cadaveric donors and those from living donors. Results are presented in Table 3. Subgroup results revealed that among patients with cadaveric donor kidneys, the use of GDT protocols was linked

to lower serum creatinine levels on postoperative days 1 and 3 (MD -1.59 mg.dL⁻¹, 95% CI -2.82 to -0.37 , $P=0.01$ and MD -1.57 mg.dL⁻¹, 95% CI -3.08 to -0.07 , $P=0.04$, respectively; $X^2=5.62$, $P=0.02$ and $X^2=4.17$, $P=0.04$, respectively). However, no such association was found among patients who received kidneys from living donors on postoperative day 0 ($X^2=1.14$, $P=0.29$) and day 7 ($X^2=2.83$, $P=0.09$). This subgroup analysis did not find any differences in other studied outcomes, including the postoperative incidence of haemodialysis, tissue oedema, respiratory complications and urine output on postoperative day 1.

Subgroup analyses were also conducted to compare outcomes between patients who were treated with fluid therapy alone versus a combination of fluids and vasoactive and/or inotropic agents. These results are presented in Table 4. There was no statistical difference in the outcomes studied, which included incidence of postoperative haemodialysis, volume of intraoperative fluids used, and MAP at reperfusion.

The results of the subgroup analysis comparing oesophageal Doppler monitoring with arterial waveform analysis are presented in Table 5. Arterial waveform analysis was associated with a lower likelihood of postoperative haemodialysis compared with conventional monitoring (RR 0.35, 95% CI 0.17–0.69, $P=0.002$. $X^2=8.43$, $P=0.004$). No such difference in postoperative haemodialysis was observed in the oesophageal Doppler monitoring group compared to the conventional monitoring group ($P=0.42$). Oesophageal Doppler monitoring led to significantly higher urine output on postoperative day 3 compared with conventional fluid therapy (MD 0.49 L, 95% CI 0.26–0.72, $P<0.0001$). However, there was no significant difference in urine output between arterial waveform analysis and conventional therapy ($P=0.82$). Patients monitored by arterial waveform analysis received less intraoperative fluids than the control group (MD -324.44 mL, 95% CI -567.61 to -81.28 , $P<0.009$). However, the overall subgroup difference was not significant ($X^2=0.36$, $P=0.55$). No statistical subgroup differences were found in other analysed outcomes, including postoperative incidence of tissue oedema, respiratory complications and serum creatinine levels.

DISCUSSION

Limited published literature exists on the use of GDT in renal transplantation surgeries. Previous studies in non-renal surgeries have demonstrated positive postoperative outcomes with GDT, but they varied in patient populations, protocols, monitoring devices and outcome measures.³¹⁻⁴⁰

Table 3. Results of subgroup analysis between living and cadaveric donors.

Outcomes ^a	Living donor					Cadaveric donor					
	No. of studies	GDT (no. of subjects)	Control (no. of subjects)	MD or RR (95% CI)	P value	No. of studies	GDT (no. of subjects)	Control (no. of subjects)	MD or RR (95% CI)	P value	Subgroup analysis
Postoperative haemodialysis	2	145	144	RR 1.13 (0.55 to 2.34)	0.73	2	46	43	RR 1.02 (0.50 to 2.06)	0.96	$\chi^2 = 0.04$ $P = 0.84$
Tissue oedema ^b	2	145	144	RR 0.27 (0.09 to 0.88)	0.03	1	19	20	RR 0.42 (0.09 to 1.92)	0.26	$\chi^2 = 0.19$ $P = 0.66$
Respiratory complications ^c	2	145	144	RR 0.14 (0.02 to 1.10)	0.06	1	26	24	RR 1.85 (0.18 to 19.08)	0.61	$\chi^2 = 2.65$ $P = 0.10$
POD serum creatinine, mg.dL ⁻¹	2	145	144	MD -0.09 (-0.60 to 0.42)	0.73	2	45	44	MD -0.85 (-2.13 to 0.44)	0.20	$\chi^2 = 1.14$ $P = 0.29$
POD 1 serum creatinine, mg.dL ⁻¹	2	145	144	MD -0.05 (-0.40 to 0.30)	0.78	2	45	44	MD -1.59 (-2.82 to -0.37)	0.01	$\chi^2 = 5.63$ $P = \mathbf{0.02}$
POD 3 serum creatinine, mg.dL ⁻¹	2	145	144	MD 0.02 (-0.22 to 0.25)	0.88	2	45	44	MD -1.57 (-3.08 to -0.07)	0.04	$\chi^2 = 4.17$ $P = \mathbf{0.04}$
POD 7 serum creatinine, mg.dL ⁻¹	2	145	144	MD 0.02 (-0.24 to 0.27)	0.90	2	45	44	MD -1.21 (-2.61 to 0.19)	0.09	$\chi^2 = 2.82$ $P = 0.09$
POD 1 urine output, L	1	110	104	MD 0.25 (-0.18 to 0.68)	0.26	1	19	20	MD 0.57 (-0.62 to 1.76)	0.35	$\chi^2 = 0.25$ $P = 0.62$

CI: confidence interval; MD: mean difference; POD: postoperative day; RR: risk ratio

^a Random-effect for all analyses.^b Clinical and/or radiological signs of excessive fluid accumulation.^c Need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure. Values in bold are statistically significant.

Table 4. Results of subgroup analysis between optimisation of cardiac output using fluids alone versus fluid and inotropes.^a

Outcomes ^b	Fluid alone					Fluid and inotropes					
	No. of studies	GDT (no. of subjects)	Control (no. of subjects)	MD or RR (95% CI)	P value	No. of studies	GDT (no. of subjects)	Control (no. of subjects)	MD or RR (95% CI)	P value	Subgroup analysis
Postoperative haemodialysis	2	55	59	RR 0.47 (0.11 to 1.95)	0.30	4	143	140	RR 0.45 (0.13 to 1.54)	0.20	X ² = 0.00 P = 0.98
Intraoperative fluids, mL	3	164	164	MD -1286.72 (-3515.43 to 941.98)	0.26	4	143	140	MD -183.97 (-553.68 to 185.73)	0.33	X ² = 0.92 P = 0.34
Intraoperative MAP reperfusion, mmHg	3	164	159	MD -1.47 (-3.75 to 0.82)	0.21	2	84	83	MD -1.57 (-4.09 to 0.94)	0.22	X ² = 0.00 P = 0.95

CI: confidence interval; MAP: mean arterial pressure; MD: mean difference; RR: risk ratio.

^a No statistical differences were found in outcomes.^b Random-effect for all analyses.

Table 5. Results of subgroup analysis between monitoring using oesophageal Doppler monitoring versus arterial waveform analysis.^a

Outcomes ^b	Arterial waveform analysis					Oesophageal Doppler monitoring					
	No. of studies	GDT (no. of subjects)	Control (no. of subjects)	MD or RR (95% CI)	P value	No. of studies	GDT (no. of subjects)	Control (no. of subjects)	MD or RR (95% CI)	P value	Subgroup analysis
Postoperative haemodialysis	5	172	175	RR 0.35 (0.17 to 0.69)	0.002	2	136	128	RR 1.24 (0.74 to 2.08)	0.42	X ² = 8.43 P = 0.004
Tissue oedema ^c	3	87	93	RR 0.31 (0.08 to 1.26)	0.10	1	110	104	RR 0.26 (0.07 to 0.99)	0.05	X ² = 0.03 P = 0.86
Respiratory complications ^d	3	117	121	RR 0.45 (0.11 to 1.84)	0.26	2	136	128	RR 0.43 (0.02 to 10.41)	0.61	X ² = 0.00 P = 0.99
POD 0 serum creatinine, mg.dL ⁻¹	4	138	143	MD -0.41 (-0.88 to 0.06)	0.08	2	136	128	MD -0.06 (-0.71 to 0.59)	0.86	X ² = 0.74 P = 0.39
POD 1 serum creatinine, mg.dL ⁻¹	5	171	176	MD -0.24 (-1.16 to 0.68)	0.61	2	136	128	MD -0.33 (-1.32 to 0.65)	0.51	X ² = 0.02 P = 0.89
POD 3 serum creatinine, mg.dL ⁻¹	4	136	141	MD -0.42 (-1.50 to 0.65)	0.44	2	136	128	MD -0.17 (-0.86 to 0.53)	0.64	X ² = 0.15 P = 0.70
POD 7 serum creatinine, mg.dL ⁻¹	4	136	141	MD -0.64 (-1.40 to 0.11)	0.09	2	136	128	MD -0.06 (-0.65 to 0.53)	0.85	X ² = 1.44 P = 0.23
POD 3 urine output, L	2	82	81	MD -0.03 (-0.28 to 0.22)	0.82	1	110	104	MD 0.49 (0.26 to 0.72)	<0.0001	X ² = 8.8 P = 0.003
Intraoperative fluids, mL	5	175	179	MD -324.44 (-567.61 to -81.28)	<0.009 ^e	2	136	128	MD -1377.68 (-4786.31 to 2030.96)	0.43	X ² = 0.36 P = 0.55
Intraoperative MAP at reperfusion, mmHg	3	142	141	MD -1.28 (-3.46 to 0.89)	0.25	1	110	104	MD -1.83 (-4.49 to 0.83)	0.18	X ² = 0.10 P = 0.76

CI: confidence interval; MAP: mean arterial pressure; MD: mean difference; POD: postoperative day; RR: risk ratio

^a Postoperative haemodialysis was less likely compared with conventional therapy when arterial waveform analysis methods were used (P=0.002). There was significantly higher urine output on POD 3 in the oesophageal Doppler monitoring group compared with conventional fluid therapy (P<0.0001).^b Random-effect for all analyses.^c Clinical and/or radiological signs of excessive fluid accumulation.^d Need for postoperative supplemental oxygen, prolonged mechanical ventilation, acute respiratory distress syndrome, and/or respiratory failure.^e Overall analysis and subgroup analysis not significant.

Values in bold are statistically significant.

This systematic review and meta-analysis aimed to comprehensively assess the effect of GDT on postoperative outcomes specifically in renal transplantation recipients.

While overall analysis showed that GDT did not result in significant differences in postoperative markers of renal function, subgroup analyses revealed potential renal protective benefits. This aligns with previous meta-analyses by Brienza et al. (2009) and Giglio et al. (2019), which reported that GDT improved postoperative renal outcomes in patients undergoing non-renal transplantation surgery.^{41,42} Such renal advantages have been attributed to GDT's principle of individualising fluid management based on flow-related parameters to maintain tissue perfusion while minimising over-hydration. This is particularly relevant in the context of renal transplantation, where ischaemia-induced graft endothelial glycocalyx degradation occurs, especially in cadaveric renal transplantation with prolonged cold ischaemic insults. This degradation leads to heightened vascular permeability and interstitial oedema, making newly transplanted grafts more susceptible to tissue oedema and venous congestion caused by over-hydration. These complications have been associated with graft dysfunction.⁴³⁻⁴⁷

Renal benefits may be implied from our subgroup analysis, which found that cadaveric renal transplantations using GDT protocols had lower serum creatinine levels in the early post-operative periods. A review of 100,000 renal transplantations by First et al. (2003) established a correlation between 6- and 12-month serum creatinine levels and annual rates of graft loss.⁴⁸ While correlation between immediate postoperative serum creatinine levels and long-term graft outcomes are not yet well-established,⁴⁸ serum creatinine levels in the immediate postoperative period may still offer insights into intraoperative graft perfusion. This assessment allows us to observe graft function before the influence of postoperative factors becomes evident.⁴⁹

Another finding suggesting potential renal benefits of GDT emerged from our subgroup analysis comparing different GDT modalities. Patients monitored with arterial waveform analysis methods had lower incidences of postoperative haemodialysis compared to those receiving conventional therapy. This outcome has been recognised as a significant prognostic consideration for long-term graft function.⁵⁰ However, oesophageal Doppler monitoring did not yield similar findings, suggesting that not all GDT modalities are equally effective. This discrepancy may be attributed to the disadvantages of

oesophageal Doppler monitoring, such as its operator-dependence and labour-intensiveness in comparison with arterial waveform analysis.⁵¹

The subgroup analysis also demonstrated that patients using oesophageal Doppler monitoring had higher urine output on postoperative day 3 compared to conventional therapy, while no significant difference was found in the arterial waveform analysis group. The result is difficult to interpret, as postoperative urine output is also confounded by postoperative fluid management, and has weak correlation to long-term renal function.⁵²

Our overall analysis found a significant association ($P=0.01$) between the implementation of GDT protocols and reduced incidences of postoperative tissue oedema in renal transplantation recipients. This further supports the notion that GDT protocols can be tailored to effectively provide appropriate fluid administration for patients in need, while preventing excessive fluid intake in others. In a study by Prasad et al. (2021) focusing on non-renal transplantation surgery, GDT was also found to decrease the incidence of tissue oedema.⁵³ This finding has clinical relevance, as our review also found lower occurrences of respiratory complications when GDT protocols were employed ($P=0.003$).

The MAP at reperfusion was similar between the GDT and conventional therapy protocols, indicating that GDT effectively maintains adequate tissue perfusion. In terms of total intraoperative fluids used, our review did not reveal statistically significant differences between the protocols. However, the absolute volume of fluid used does not fully account for other factors, such as the patient's weight, preoperative fasting protocols, underlying comorbidities and duration of surgery.

A meta-analysis of adult patients undergoing major surgery by Giglio et al. (2019) attributed the lower incidence of postoperative acute kidney injury in GDT protocols to the synergistic utilisation of fluid therapy and inotropes.⁴² However, our subgroup analysis that examined the administration of fluid alone versus a combination of fluids and/or inotropes revealed no significant differences in outcomes analysed. Such observed benefits may be context-dependent. Fluid protocols vary greatly based on the patient's characteristics, such as in a renal transplantation recipient. Our findings suggest that unexamined factors, such as differences in GDT protocol guidelines, may influence the observed benefits. Moreover, limitations in the subgroup analysis, including small study populations and heterogeneity in dose and

timing of fluids and vasopressors/inotropic agents, should be considered.

There are several limitations to this systematic review and meta-analysis. The primary challenge lies in the heterogeneity of included studies, with variations in baseline patient characteristics (e.g. duration of preoperative renal replacement therapy and type of immunosuppressant therapy), donor kidney type, haemodynamic monitoring methods and fluid optimisation protocols. While subgroup analyses were performed to address these variables, they were not able to adjust for all confounding factors. Furthermore, definition of outcome measures varied among included studies. This could have weakened statistical associations and was considered during the assessment of the quality of evidence of our results. Future studies could identify target- and study-specific patient-centred postoperative outcomes instead.

Another limitation is the small number of available studies on GDT in renal transplantation surgeries, resulting in potential publication bias despite efforts to include all relevant published reports. The current literature in this area remains limited, and the inclusion of studies with small sample sizes and non-randomised designs may introduce biases. For example, the non-randomised controlled study by Srivastava et al. (2015) significantly influenced the analysis of postoperative tissue oedema and respiratory complications, raising concerns about potential blinding bias.²⁹ Other sources of bias to be addressed should be in the blinding of clinicians not directly involved in the intervention, including those measuring postoperative outcomes.

Further investigation into graft quality is warranted as it presents another confounding factor. While our subgroup analysis does account for differences between living versus cadaveric grafts, this comparison may be more complex. Grafts from living donors and standard criteria cadaveric donors are expected to have lower rates of delayed graft function, while grafts from extended criteria cadaveric donors and renal donation after cardiac death often suffer from higher rates of delayed graft function. GDT protocols may be particularly advantageous in such groups of renal transplantation recipients and can be further explored.

Moreover, continuous cardiac output monitoring may be advantageous in complex fluid management during renal transplantation surgeries. Renal transplantation recipients undergo a triphasic approach to fluid management, transitioning from preoperative fluid restriction to intraoperative directed fluid therapy for euvolaemia, followed by relative over-hydration in the immediate postoperative period. Continuously striking this

balance in real-time can potentially optimise graft survival, and reduce tissue oedema and respiratory complications.

However, present experimental studies are not standardised to achieve specific consensus on what is the ideal protocol to direct fluid therapy and what modality of monitoring is best suited to achieve it. With more renal transplantations in the past decade being done without placement of invasive lines, along with increased use of minimally invasive strategies to measure cardiac output, the convention of what contributes to the goal of directed fluid therapy needs reappraisal. Future initiatives for GDT can commence in the preoperative period and continue meticulously from the intraoperative period to the postoperative phase, where the operating surgical team, anaesthesiologists and renal physicians work collaboratively to achieve a smooth transition in care of renal transplantation recipients.

CONCLUSION

Few studies have explored the benefits of GDT in renal transplantation surgeries. This review highlights that renal transplantation recipients may benefit from judicious fluid management using GDT. Within the limitations of existing data, the review showed that intraoperative GDT protocols may offer benefits in postoperative outcomes, with potential renal protective benefits, lower incidences of tissue oedema and respiratory complications in renal transplantation recipients. However, care must be taken before definite conclusions can be made as renal protective benefits were only seen in subgroup analysis while no such findings were found in the overall analysis. Future randomised controlled studies need to address several important limitations. These include the need for standardised reporting of outcome measures to improve consistency and comparability across studies. In addition, the impact of specific aspects of GDT, such as the method of monitoring cardiac output, strategies for optimising cardiac output, and variations in therapeutic goals should be explored. It is also crucial to account for confounding factors and potential sources of bias to obtain more accurate and reliable results. These areas of focus will contribute to enhancing the quality and reliability of research in this field.

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