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Goal-Directed Haemodynamic Therapy Improves Patient Outcomes in Kidney Transplantation

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Abstract

Introduction: Kidney transplant graft function depends on optimised haemodynamics. However, high fluid volumes risk hypervolaemic complications. The Edwards Lifesciences ClearSight™ device permits fluid titration through markers of preload and beat-to-beat blood pressure monitoring. We evaluated the implementation of a novel goal-directed haemodynamic therapy protocol to determine whether patient outcomes had improved. **Design:** A retrospective evaluation of standard care versus goal-directed haemodynamic therapy in adults undergoing kidney transplantation was performed in a single centre between April 2016 and October 2019. Twenty-eight standard-of-care patients received intraoperative fixed-rate infusion and 28 patients received goal-directed haemodynamic therapy. The primary outcome was volume of fluid administered intraoperatively. Secondary outcomes included blood product and vasoactive drug exposure, graft and recipient outcomes. **Results:** Intraoperative fluid administered was significantly reduced in the goal-directed haemodynamic therapy cohort (4325 vs 2751 ml, $P < .001$). Exposure to vasopressor (67.9% vs 42.9%, $P = .060$) and blood products (17.9% vs 3.6%, $P = .101$) was unchanged. Immediate graft function (82.1% vs 75.0%, $P = .515$), dialysis requirement (14.3% vs 21.4%, $P = .729$) and creatinine changes post-operatively were unchanged. In the goal-directed haemodynamic therapy cohort, 1 patient had pulmonary oedema (3.6%) versus 21.4% in the standard cohort. Patients in the goal-directed haemodynamic therapy group were more likely to mobilise within 48 hours of surgery (number needed to treat = 3.5, $P = .012$). **Conclusions:** Protocolised goal-directed haemodynamic therapy in kidney transplantation was safe and may improve patient, graft, and surgical outcomes. Clinical trials assessing goal-directed approaches are needed.

Keywords

kidney transplant, anaesthesia, goal-directed therapy, perioperative care, cardiac output, enhanced recovery, renal transplant

Introduction

Kidney transplant recipients are vulnerable to intraoperative haemodynamic derangement, which increases the risk of delayed graft function (DGF), leading to poorer long-term outcomes.[1] Optimised graft perfusion reduces the risk of hypovolaemia and DGF as well as post-operative complications due to hypervolaemia.[2]

Perioperative goal-directed haemodynamic therapy in major surgery optimises end-organ oxygen delivery and minimises complications.[2] Anaesthetic care in kidney transplantation is highly heterogeneous.[3] The commonest approach to quantisation of fluid status involves measurement of the central venous pressure[3] (CVP) with some evidence of efficacy.[4,5] However, there are limited data supporting a change in CVP as a marker of fluid responsiveness.[2]

The Edwards Lifesciences ClearSight™ device is a non-invasive finger cuff that uses the volume-clamp method to continuously measure blood pressure and may permit improved haemodynamic optimisation than CVP, while avoiding the harm associated with arterial lines. Our institution implemented an intraoperative ClearSight™-guided goal-directed haemodynamic therapy protocol to optimise intravenous fluid administration and reduce associated complications in kidney transplantation.

To evaluate the change in care, we compared two cohorts: one receiving standard of care with CVP-guided fixed-rate fluid infusions and the other, ClearSight™-guided goal-directed haemodynamic

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therapy. The primary outcome was the volume of intravenous fluid administered.

Methods

Design and Setting

This evaluation was a retrospective assessment of a change in standard of care for kidney transplant patients at a large-volume centre. The need for ethical approval and written consent was waived by the local research and development office; the study was registered as a service evaluation.

Population

Thirty-three percent of the centre's kidney transplant waiting list is female, 26% were aged 35-49 years, 28% 50-59 years and 25% 60-69 years.[6] The primary kidney disease was diabetes in 23% of patients and hypertension/renovascular disease in 12%. Thirty-seven percent were white ethnic background, 30% Asian, 26% black and 7% other.

Sampling

All adult patients undergoing deceased donor kidney transplantation between April 2016 and March 2017 were included in the standard cohort. Following goal-directed haemodynamic therapy implementation, the ClearSight™ cohort constituted deceased donor transplants between April 2018 and October 2019. Patients with incomplete datasets were excluded.

Conduct of Anaesthesia

Patients were dialysed pre-operatively at the discretion of the nephrologist. Patients were anaesthetised using either alfentanil 10 mcg/kg or fentanyl 1-2 mcg/kg followed by propofol or thiopentone to effect. Muscle relaxation with atracurium 0.5 mg/kg or rocuronium 0.6 mg/kg was followed by endotracheal intubation and maintenance of anaesthesia with volatile agents. Volume control ventilation provided a consistent tidal volume. An internal jugular central venous catheter was placed in all patients. A diuretic was not used in either group.

Standard Care Cohort

A fixed rate fluid infusion using Haemosol was administered at 20-30 ml/kg/hr. Fluid boluses were administered to maintain a CVP that the anaesthetist deemed appropriate with an upper threshold of 17 cm H_2O whereupon the infusion rate was reduced. Systolic blood pressure was maintained at or above 110 mm Hg. The primary vasoactive agent was ephedrine followed by phenylephrine infusion.

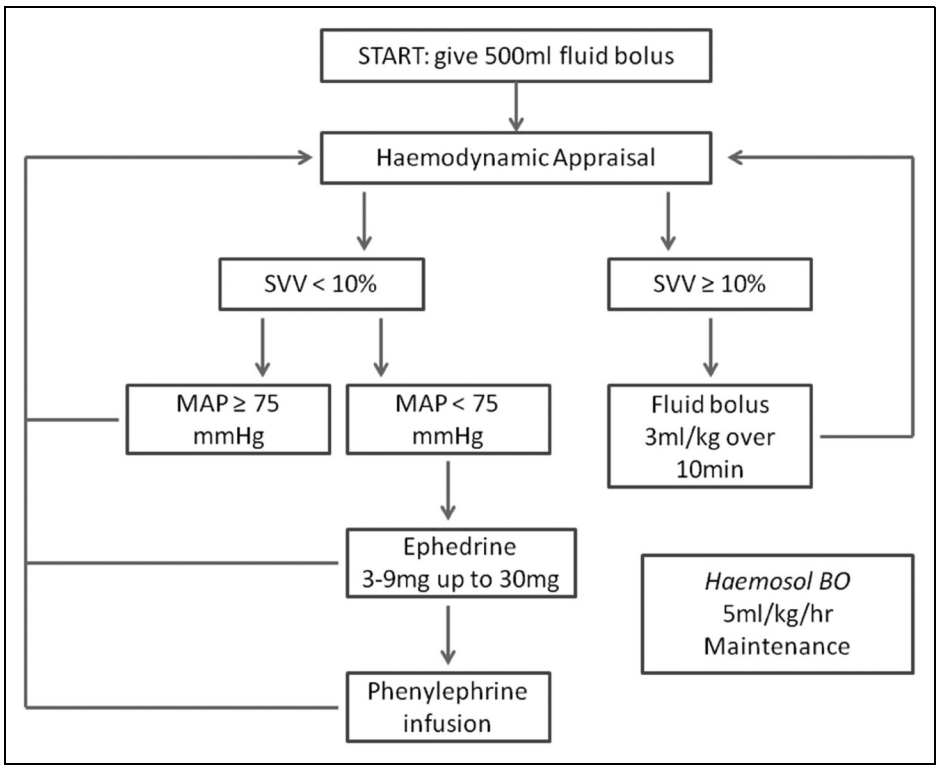

Figure 1. ClearSight™ Goal-Directed Haemodynamic Therapy Protocol Implemented Intraoperatively. SVV, stroke volume variation; MAP, mean arterial blood pressure

ClearSight™ Protocol Cohort

Following a review of the published literature and expert multidisciplinary consensus, a goal-directed haemodynamic therapy protocol was developed (**Figure 1**), aiming for a low stroke volume variation (SVV) and high mean arterial pressure (MAP) state to optimise blood flow with an appropriate peripheral resistance.

The ClearSight™ device was attached to the patient preoperatively. A 500-ml bolus of Haemosol was administered followed by a maintenance infusion of 5 ml/kg/hr. After initiation of controlled ventilation, the SVV was measured; if the SVV was greater than 10%, a 3-ml/kg fluid bolus was administered. If the SVV was below 10% and the MAP was under 75 mm Hg, vasoactive drugs (ephedrine then phenylephrine) were given. Cycles of haemodynamic appraisal were continually performed until the end of surgery.

Outcomes

The primary outcome was the volume of intravenous fluid administered intraoperatively. Secondary outcomes included the exposure to blood products and vasoactive agents, the incidence of DGF, the time to graft function, and creatinine levels on post-operative days 1, 7 and 90. Further outcomes were the incidence of postoperative pulmonary oedema, blood transfusion up to post-operative days 3 and 7, change in body weight on post-operative day 1, length of hospital stay, postoperative ileus and early mobilisation.

Definitions

Ileus was defined as a lack of bowel sounds on post-operative day 1, early mobilisation as sitting out of the bed by postoperative day 2. The need for blood transfusion was left to clinician discretion. The presence of pulmonary oedema was defined as clinical signs or radiographical evidence combined with the need for supplemental oxygen within 72 hours postoperatively, in the absence of another aetiology. DGF was defined as the need for dialysis within the first post-operative week. Time to graft function was defined as days until creatinine improvement, diuresis, and no need for dialysis.

Data Collection

Data collection occurred in the operating room, from the ward during the inpatient stay, from clinic visits until 90 days postoperatively, and retrospectively from clinical and nursing notes.

Data were collected on patient demographics, comorbidities, renal characteristics, and graft donor characteristics. Intraoperative variables (case duration, fluid, blood product and vasoactive agent administration, CVP and MAP data were extracted from the anaesthetic record. SVV and MAP data were extracted from the ClearSight™ device. Graft function data were obtained up to 90 days postoperatively. The presence of pulmonary oedema was recorded up until postoperative day 7, or until discharge, whichever was sooner.

Data Analysis

The data were assessed for normality using the Kolmogorov–Smirnov test with Lilliefors significance correction. The Student's t, Mann–Whitney U, Pearson Chi-squared and Fisher's exact tests were applied, as appropriate. Correlations were performed using Spearman rank correlation. Data are presented as mean (standard deviation), median [25%, 75% quartile] or count (population percentage).

A post hoc power calculation (effect size vs sample size) for the primary outcome was performed using a two-tailed independent samples t-test with an α error of 0.05, generating a power of 0.93. Data were transcribed into Microsoft Excel, cleaned and checked before transfer into SPSS version 25 (IBM, New York, USA) for statistical analysis.

Results

Demographic Characteristics

Retrospective data were obtained from 28 patients in the standard care group and 28 patients managed using the ClearSight protocol. The predominant aetiologies of renal dysfunction in both patient cohorts were diabetes, hypertension, and IgA nephropathy (**Table 1**). The ClearSight cohort had higher pre-transplant creatinine values (median difference 224 μg/ml, $P = .008$) and trended towards more frequently being on dialysis (85.7% vs 60.7%, $P = .068$).

Intraoperative Outcomes

Mean case-averaged MAP (mean difference 1 mm Hg) was comparable. The CVP was higher in the Standard Care group than the ClearSight cohort (mean difference 2.1 mm Hg, $P = .006$). The average SVV in each ClearSight case had a mean of 8.5 (2.7)%.

The total crystalloid volume infused was significantly reduced in the ClearSight™ group (4109 (1894) versus 2751 (1177), $P < .001$). Similarly, total intravenous volume administered was significantly reduced (4325 vs 2751 ml, $P < .001$; data not shown). This difference remained when adjusted for patient body weight and case duration (14.2 (6.6) vs 9.3 (4.9) ml/kg/hr, $P = .003$).

Intraoperatively there was a trend towards lower patient exposure to blood products (21.4% vs 3.6%, $P = .101$). There was no correlation between pre-operative haemoglobin levels and intra- or post-operative transfusion. Patient exposure to sodium chloride was reduced (relative risk reduction 80%, $P = .004$; data not shown). Patient exposure to vasopressors was unchanged; although ClearSight™ patients had an overall lower exposure to any vasoactive agent, this was not significant (67.9% vs 42.9%, $P = .060$). See **Table 2**.

Table 1. Characteristics of Kidney Graft Recipients and Organ Donors in the Standard of Care and ClearSight Groups.

Recipient characteristics		Standard Care Group $N = 28$ **Mean (SD)**	ClearSight Group $N = 28$ **Mean (SD)**	*P* value
Age, year		54 (14)	55 (11)	.683[a]
Pre-operative body mass, kg		72.4 (17.7)	74.8 (12.1)	.561[a]
		***N* (%)**	***N* (%)**	
Female sex		7 (25.0%)	12 (42.9%)	.259[b]
Heart failure		4 (14.3%)	2 (7.1%)	.669[d]
Diabetes		7 (25.0%)	12 (42.9%)	.259[b]
Hypertension		20 (71.4%)	22 (78.6%)	.758[b]
Ethnicity	White	13 (46.4%)	8 (28.6%)	.304[b]
	Black	10 (35.7%)	11 (39.3%)	
	Other	5 (17.8%)	9 (22.1%)	
On dialysis		17 (60.7%)	24 (85.7%)	.068[b]
		Mean (SD)	**Mean (SD)**	
Pre-operative haemoglobin (g/dl)		117 (12)	111 (10)	.076[a]
		Median [IQR]	**Median [IQR]**	
Pre-operative creatinine (μg/ml)		539 [428, 761]	763 [537, 1018]	.008[c]
Donor characteristics		STD Group	CS Group	*P* value
		***N* = 28**	***N* = 28**	
Organ source	DBD	21 (75.0%)	17 (60.7%)	.391[b]
	DCD	7 (25.0%)	11 (39.3%)	
Donor acute kidney injury		5 (17.9%)	5 (17.9%)	1.000[b]
		Mean (SD)	**Mean (SD)**	
Cold ischaemic time (hours)		13.1 (3.7)	12.8 (5.2)	.804[a]
Donor age (years)		49 (16)	51 (16)	.651[a]
		Median [IQR]	Median [IQR]	
Donor creatinine (μg/ml)		76 [61, 85]	84 [63, 103]	.323[c]

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death.
[a]Independent samples *t*-test, two-tailed, equal variances not assumed (Levene's test $P > .05$).
[b]Pearson Chi-squared test, two-sided.
[c]Mann–Whitney *U* test.
[d]Fisher's exact test, two-tailed.

Posttransplant Outcomes and Complications

There were no differences in immediate graft function between the two groups (82.1% vs 75.0%, $P = .515$) or the need for post-operative dialysis (14.3% vs 21.4%, $P = .729$). Patients in the ClearSight™ cohort had higher pre-operative creatinine level than the standard care group (763 vs 539 μg/ml, $P = .008$) and this difference persisted into the first postoperative day (631 vs 439 μg/ml, $P = .008$). Subsequently, ClearSight™ patients recovered their renal function more rapidly and to a greater extent (79% vs 75% improvement, $P = .042$), hence by postoperative day 90 there was no difference in creatinine (133 vs 148 μg/ml, $P = .676$).

The incidence of postoperative pulmonary oedema in the standard care group was 21.4% while a single event occurred in the ClearSight™ group (3.6%). Patients who developed postoperative pulmonary oedema received higher intraoperative fluid volumes (4815 vs 3356 ml, $P = .051$; data not shown). The need for blood product transfusion within 72 hours or 1 week of surgery was comparable between the two cohorts, as was length of hospital stay. Patients in the ClearSight group were more likely to mobilise within 48 hours of surgery (number needed to treat = 3.5, $P = .012$) and trended towards less weight gain in the first 24 hours post-operatively (mean difference 1.4 kg, $P = .052$). See **Table 2**.

Discussion

A protocolised approach to fluid and vasoactive agent management in kidney transplantation, guided by a non-invasive cardiac output monitor, led to a significant reduction in fluid administration without impairing haemodynamic stability or kidney graft outcomes up to 90-day postoperatively. These changes were associated with improved rates of mobilisation and a trend towards reduced body weight gain at 24 hours. These findings were in keeping with titration of fluid therapy to timepoints when the patient was fluid responsive rather than a continuous high-volume infusion irrespective of patient

Table 2. Intraoperative, Patient and Renal Graft Outcomes in the Standard of Care Control and ClearSight Intervention Groups.

		Standard Care Group $N = 28$	ClearSight Group $N = 28$	P value
Intraoperative		**Mean (SD)**	**Mean (SD)**	
Total crystalloid volume (ml)		4,109 (1,894)	2,751 (1,177)	.001[a]
Total intravenous volume (adjusted) (ml/kg/hr)		14.2 (6.6)	9.3 (4.9)	.003[a]
Mean MAP (mm Hg)		82.6 (9.1)	82.6 (8.6)	.675[a]
Mean CVP (mm Hg)		13.4 (4.1)	10.5 (2.8)	.006[a]
		***N* (%)**	***N* (%)**	
Gelofusin/normal saline exposure		12 (42.9%)	2 (7.1%)	.004[c]
Exposure to any vasopressor		19 (67.9%)	12 (42.9%)	.060[b]
Intra-operative blood product exposure		6 (21.4%)	1 (3.6%)	.101[c]
Immediate function		23 (82.1%)	21 (75.0%)	.515[b]
Graft outcomes		**Median [IQR]**	**Median [IQR]**	
Delay in function (days)		6 [2, 13]	7 [5, 10]	.755[d]
Need for post-operative dialysis		4 (14.3%)	6 (21.4%)	.729[c]
Pre-operative creatinine (μg/ml)		539 [428, 761]	763 [537, 1018]	.008[d]
Post-op Day 1	Creatinine (μg/ml)	439 [290, 761]	631 [457, 811]	.003[d]
	Creatinine change (%)	22 [7, 50]	11 [4, 26]	.169[d]
Post-op Day 7	Creatinine (μg/ml)	187 [135, 412]	288 [174, 633]	.091[d]
	Creatinine change (%)	64 [38, 77]	56 [37–80]	.544[d]
Post-op Day 90	Creatinine (μg/ml)	133 [113, 171]	148 [107, 196]	.676[d]
	Creatinine change (%)	75 [66, 81]	79 [72, 87]	.042[d]
		***N* (%)**	***N* (%)**	
Pulmonary oedema		6 (21.4%)	1 (3.6%)	.101[c]
Blood transfusion within 72 hours		8 (28.6%)	2 (7.1%)	.078[c]
Blood transfusion within 7 days		10 (35.7%)	6 (21.4%)	.237[b]
Post-operative ileus		7 (25.0%)	3 (10.7%)	.295[c]
Mobilisation within 48 hours		19 (67.9%)	27 (96.4%)	.005[b]
		Mean (SD)	**Mean (SD)**	
Body weight gain (kg) at 24 hours		5.5 (2.6)	4.1 (2.5)	.052[a]
		Median [IQR]	**Median [IQR]**	
Length of hospital stay (days)		6 [5, 11]	7 [6, 9]	.290[d]

Abbreviations: MAP, mean arterial pressure; CVP, central venous pressure.
[a]Independent samples *t*-test, two-tailed, equal variances not assumed (Levene's test $P > .05$).
[b]Pearson Chi-squared test, two-sided.
[c]Fisher's exact test, two-sided.
[d]Mann–Whitney *U* test.

and surgical status. The CVP was lower in the ClearSight™ cohort suggesting that targeting high CVP values was unnecessary.

Despite the ClearSight™ cohort having been in more severe renal failure with a trend towards being more anaemic and more likely to be on dialysis, these patients improved to a greater extent by 90-day postoperatively than the standard care group. This improvement was likely multifactorial, including a reduction in postoperative renal oedema.

Despite the improvements seen in patient-orientated outcomes, no improvement in length of hospital stay was found. Explanations include the small study sample size and higher pre-operative creatinine and dialysis rates in the ClearSight™ cohort.

Transfusion was not protocolised but a trend towards lower rates of blood transfusion at 72-hour postoperatively was observed. This was likely to be related to a reduction in iatrogenic haemodilution. Lower rates of peri-operative blood transfusion may associate with improved graft outcomes and patient survival following renal transplantation.[7]

The findings are in keeping comparable studies in perioperative kidney transplant management. Halawa demonstrated that an enhanced recovery package improved patient mobilisation, enteral intake and reduced hospital stay.[8] Cavaleri found that a pulse contour-directed approach to intravenous fluid administration reduced post-operative ileus.[9] Srivastava demonstrated that a transoesophageal Doppler-compared to CVP-guided approach led to a reduction in fluid administration, colloid exposure, post-operative tissue and pulmonary oedema.[10]

This evaluation was subject to the usual caveats of retrospective data collection. As this was an assessment of a new standard of care no sample size calculation was performed and case numbers were time-justified. Lack of randomisation, as well as the spread of patient cohorts across several years, means that other changes to patient care may have occurred. However, data were collected on a broad range of risk factors

and demonstrated that the 2 study cohorts were statistically similar, although there was not complete access to data for all components of the Kidney Donor Risk Index. Other anaesthetic and surgical care remained unchanged during the evaluation period.

Conclusion

The implementation of a ClearSight™-guided goal-directed haemodynamic therapy protocol led to improvements in a range of outcomes that are meaningful to patients and clinicians following kidney transplantation. Prospective randomised controlled trials are needed to provide robust clinical evidence to support this approach and determine health economic and patient quality of life benefits.

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Declaration of Conflicting Interests

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