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BENEFITS OF MULTIMODAL ENHANCED RECOVERY PATHWAY IN PATIENTS UNDERGOING KIDNEY TRANSPLANTATION

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Abstract Body

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Abbreviations:

KTX, kidney transplant

DGF, delayed graft function

KDPI, kidney donor profile index

BMI, body mass index

CPRA, calculated panel reactive antibody

IQR, interquartile range

SD, standard deviation

OR, odds ratio

CI, confidence interval

ATG, antithymocyte globulin

ECMC, erie county medical center

LOS, length of stay

ERAS, enhanced recovery after surgery

ABSTRACT

Background: Use of Enhanced recovery after surgery (ERAS) pathways to accelerate functional recovery and reduce length of stay (LOS) has rarely been investigated in kidney transplantation (KTX). **Materials and Methods:** Consecutive adult isolated KTXs between 7/2015-7/2016 (ERAS, n=139) were compared with a historical cohort between 1/2014-7/2015 (HISTORIC, n=95). **Results**: ERAS recipients were significantly more likely to receive kidneys that were non-local (56.1% vs. 4.2%), higher Kidney Donor Profile Index (36-85, 58.4% vs. 45.2%; >85, 15.2% vs. 10.7%), cold ischemia time ≥30h (62.4% vs. 4.7%), induced with antithymocyte globulin (97.1% vs. 87.4%), and to develop delayed graft function (46.4% vs. 25.0%). LOS was shorter by 1 day amongst ERAS (mean 4.59) compared to HISTORIC patients (mean 5.65) predominantly due to a shift in discharges within 3 days (32.4% vs. 4.2%). 30-day readmission to the hospital (27.3% vs. 27.4%) or emergency room visit (9.4% vs. 7.4%) were similar. There was one 30-day death in the ERAS group and none in the HISTORIC group. Return to bowel function and early meal consumption were significantly associated with ERAS; however, with somewhat higher diarrhea and emesis rates. **Conclusion**: ERAS following KTX correlated with lower LOS without change in readmissions or ER visits despite higher delayed graft function rates.

INTRODUCTION

The imbalance between kidney organ supply and demand compels many centers to transplant non-standard kidneys that require greater resource utilization as evidenced by longer length of stay,[1,2] more readmissions,[1] and increased requirement for dialysis.[1] From the perspective of the transplant program, a major obstacle to providing access to transplantation in hospitals that run at high occupancy is bed availability; decompressing inpatient beds is advantageous to facilitate inpatient throughput. In the current medical and economic climate, adopting efficient models for providing high-quality care and reducing

unnecessary inpatient resource utilization are of paramount importance across all specialties.

Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the stress response following surgery. The key elements of ERAS protocols include preoperative counseling, optimization of nutrition, short-acting anesthetics, effective opioid-sparing postoperative pain and nausea control, avoiding unnecessary invasive monitoring, early mobilization and oral nutrition.[3-6] Implementation of ERAS offers the potential of reducing length of stay (LOS) while maintaining similar or lower morbidity and increased patient satisfaction; however, few have examined ERAS after kidney transplantation.[7,8] In other areas of general surgery, robust evidence supports the benefits of ERAS over traditional postoperative care. The physiological benefits of enhanced recovery pathways for colorectal surgery patients were first shown by Henrik Kehlet,[3,9] and these pathways are now widely adopted[10-12] and included in colorectal treatment recommendations.[12] ERAS or "fast-track" programs have also become an important focus of perioperative management after vascular surgery,[13] thoracic surgery,[14] hepatic surgery,[15] oncology,[5,6] hernia repair[16] and radical cystectomy[5].

Management of kidney transplant patients is complicated and already highly protocolized in many ways; however, surgical tradition often dictates practice patterns and there is a paucity of empiric data examining management of these patients. We hypothesized that implementation of an ERAS pathway would result in faster functional recovery and shorter hospitalizations without impacting quality in patients undergoing kidney transplantation. The aim of this study was to investigate the impact of ERAS program on early functional recovery, length of postoperative hospital stay, and short-term clinical outcomes.

Materials and Methods

A retrospective cohort study of consecutive adult living- and deceased-donor kidney-only recipients at Erie County Medical Center between January 2014 and July 2016 was performed to evaluate outcomes after implementation of an ERAS pathway. There were no exclusions. Kidney transplants (KTX) performed after ERAS implementation, between July 15, 2015 and July 31, 2016 (ERAS), were compared with a historical cohort between January 1, 2014-July 14, 2015 (HISTORIC). All patients were followed up for 90 days. There was no loss to follow up.

Primary outcomes were (a) index hospitalization LOS, (b) at least one unplanned readmission or emergency room visit within 30-days after discharge from the transplant hospitalization, (c) reason for readmission or ER visit, (d) death or graft failure within 30-days after discharge from the transplant hospitalization, and (e) graft failure during transplant hospitalization. Secondary outcomes were: bowel movement by post-operative day 3, per oral intake during first or second post-operative meal, anti-emetic administration beyond post-operative day 2, emesis or diarrhea during transplant hospitalization, peak and mean pain levels on post-operative day 2, and urine leak within 90 days of transplant. LOS was calculated from the day of surgery to discharge. LOS within 3 days was defined as discharge any time during the postoperative day 3. Reasons for readmission were the presenting diagnosis that prompted admission to the hospital after discharge. Graft failure was defined as death, removal of allograft, retransplantation, or return to chronic dialysis (all-cause). Pain scores were patient reported using the 0 to 10 visual analog scale and recorded by the bedside nurse. Distance home to transplant hospital was determined by geocoding the patients' zip code to the Census Block Group level and mapping to data from the 2014 census.[18]

Clinical data was obtained from a prospectively maintained transplant database or were collected retrospectively from the electronic medical record using standardized forms from progress notes, medication administration records, medical administration notes, physician and nutrition notes, and nursing documentation.

Study Environment

Erie County Medical Center (ECMC) is a 602-bed tertiary care teaching hospital located in Buffalo, NY. It serves a population with low socioeconomic status and high disease burden (over 50% of hospital admissions have diabetes). Erie County ranks 54th in community health rankings between the 62 counties in NY State.[17] Organ availability within the ECMC donor service area dropped dramatically following organ allocation changes in December 2014 that mandated increased sharing. This relative reduced access to transplantation from deceased donors was mitigated by liberalized acceptance practices.

Use of ERAS at our institution was part of a continuous quality improvement project, so initial implementation of the pathway was a gradual process. Adherence to components of the pathway was higher for some elements that could be automatically checked within the computerized physician order entry (CPOE) whereas adherence to other components was variable among medical staff but improved over time. ERAS component differences between eras are depicted in Table 1 and adherence to the pathway is provided in Table 2. Key features of the ERAS pathway are as follows: immediate extubation after surgery, sips of water and ice chips initiated immediately when the patient is fully awake, usually 1–2 h after surgery, followed by solid food on the first post-operative morning with appropriate restrictions for diabetes and other comorbidities but without volume limitations, pre-emptive cathartic administration with castor oil on postoperative day 1, emphasis on early mobilization without barriers other than the patients baseline functional status, peripheral (rather than central) antithymocyte globulin administration, expedited completion of induction therapy (no between dose interval requirement), earlier initiation of tacrolimus at

the next scheduled interval (0600 or 1800), daily counseling given regarding expectations in terms of symptoms and progress, and an emphasis on early discharge in the absence of complications. Three months after ERAS pathway initiation, 3 additional components were changed: (1) ERAS patients with delayed graft function (DGF) received hemodialysis within the *transplant hospital unit* for a 3-4 week duration instead of immediate return to the *non-transplant nephrology unit*. Specifically, hemodialysis was scheduled for 3pm on alternating days and clinic was scheduled on the same morning (excluding Fridays) with the anticipation of cancelling dialysis or reducing the frequency as soon as the clinical picture suggested sufficient function. (2) As needed intravenous opioids were automatically discontinued after POD 1 instead of at the time of discharge. Subsequent pain treatment was with oral acetaminophen or opioids only unless intravenous opioids were re-ordered by a physician. (3) Increased utilization of infusion centers for administration of some intravenous therapies (e.g. steroids, antibiotics, immunoglobulin) in the setting of stable graft function (all antithymocyte globulin administrations were performed in the hospital). No preoperative selection criteria were applied to identify those patients who might be suitable for ERAS discharge.

Several characteristics remained the same during both eras. All patients were regularly reviewed by the multidisciplinary team on the following morning, daily, and at the planned time of discharge. The entire team was available during normal weekday work hours, but generally not weekends or holidays. Immunosuppression consisted of antithymocyte globulin or basiliximab induction along with triple maintenance tacrolimus, mycophenolate mofetil, and corticosteroid taper. Intraoperative placement of double-J ureteral stents were performed per surgeon preference. Antiemetic medication was used on demand. Patients were discharged if clinical parameters were within normal limits and they were ambulatory, able to eat, had adequate pain control on oral analgesics, and after receiving adequate home support and education. Formal comprehension testing or cognitive assessment was not performed. The patients, in both eras, were followed in the transplant

clinic within 1 to 3 days postoperatively and seen twice weekly, with laboratory assessments, during the first post-transplant month. Each recipient was given the telephone number of the transplant center and physicians are available after hours and on weekends to respond to calls. Home health care (HHC) agencies were often utilized. An outpatient observation unit was not available. A set criterion readmission policy was not used; each case was managed by either the surgeon or nephrologist as the clinical scenario dictated.

Statistical Analysis:

Recipient, donor, and transplant covariates evaluated are depicted in Table 3. The appropriate functional form of covariates were determined by exploratory data analysis in unadjusted models and perceived impact on clinical meaningfulness. Univariate associations between exposure groups were examined using the Chi-square test or Fisher's exact test for categorical variables (summarized as proportions) and Student's *t*-test for continuous variables whose distributions approximated normality (summarized as median and interquartile ranges and/or mean and standard deviation). Skewed distributions were compared with the Wilcoxon rank-sum test. All statistical analysis were conducted using the SAS system version 9.2 (SAS Institute, Inc.). All p-values were 2-sided and <0.05 was considered statistically significant. The study was approved by the University of Buffalo Institutional Review Board.

Results

There were 139 ERAS and 95 HISTORIC cases. ERAS recipients were significantly more likely to receive kidneys that were non-local (56.1% vs. 4.2%), higher Kidney Donor Profile Index (36-85, 58.4% vs. 45.2%; >85, 15.2% vs. 10.7%), cold ischemia time ≥ 30h (62.4% vs. 4.7%), induced with antithymocyte globulin (97.1% vs. 87.4%), and to develop delayed graft function (46.4% vs. 25.0%). Other demographic, donor, and transplant characteristics were similar (Table 3). Length of stay was shorter by 1 day amongst ERAS (mean 4.59; median 4) compared to HISTORIC patients (mean 5.65; median 4) predominantly due to a shift in discharges within 3 days (32.4% vs. 4.2%). Readmission

within 30 days to the hospital (27.3% vs. 27.4%) or visits to emergency room (9.4% vs. 7.4%) were similar. There was one 30-day death in the ERAS group and none in the HISTORIC group. There were 2 urine leaks within each cohort.

Secondary endpoints including return to bowel function (61.2% vs. 31.6%) and early meal consumption (44.6% vs. 12.6%) were significantly associated with ERAS relative to the HISTORIC cohort, respectively; however, with somewhat higher diarrhea (20.9% vs. 11.6%) and emesis (15.8% vs. 8.4%) rates. There were not any episodes of aspiration pneumonia following Castor Oil administration. Other between-group differences were similar including use of an anti-emetic beyond post-operative day 2 (62.6% vs. 66.3%), peak pain level on post-operative day 2 <7 (38.1% vs. 36.8%), and mean pain level on post-operative day 2 <5 (63.3% vs. 65.3%), respectively. The cumulative number of clinic visits per patient within 30 days post discharge (excluding cases readmitted during this time period) were similar between the ERAS (6.60 visits) and the HISTORIC (7.03 visits) cohorts.

Several sensitivity analyses were performed to evaluate the impact of specific elements of the ERAS pathway. LOS was lower in the ERAS cohort relative to HISTORIC even after exclusion of 29 HISTORIC and 2 ERAS patients that remained intubated following case completion (mean LOS 4.66 vs. 5.67 days, respectively) and stratification of patients without delayed graft function (mean LOS 3.99 vs. 5.36 days, respectively) or with delayed graft function (mean LOS 6.2 vs. 7.2 days, respectively)

Discussion

Recently, there has been a paradigm shift in perioperative patient care, from highly individualized care plans driven by surgeon clinical judgment and specific physiologic milestones toward a more standardized framework for specific patient groups or procedures. Although clinical decision making and experience remain paramount to successful outcomes, recent data suggest that more regimented care pathways are able to hasten recovery without increasing morbidity. Previously published literature on ERAS

pathways from other surgical disciplines informed the development and implementation of our own pathway for kidney transplantation. In this study, we demonstrated that despite higher delayed graft function rates, implementation of an ERAS pathway was associated with reduced length of stay without impacting short-term graft function, mortality, and readmission rates.

Although LOS after KTX has decreased over the years,[19] few studies have described specific pathways to achieve shorter stays or evaluated its safety. Concerns have been reasonably raised for potential increases in morbidity (e.g. by aspiration with accelerated feeding), increased readmission (with early discharge), and higher mortality (by failure to rescue due to early discharge). Two KTX studies of 45 and 46 recipients previously demonstrated that standardized postoperative care can affect reduced LOS without compromising safety.[7,8] Another protocol focusing on high-risk patients was successful in significantly reducing LOS and 30-day readmission rates (from 20% to 10%) in patients with DGF by instituting a multi-disciplinary approach to team rounds and discharge planning, outpatient clinic equipped with an infusion center, and daily nurse visits of patients with DGF.[20] Our ERAS protocol was associated with reduced LOS without impacting safety by focusing on early feeding, pre-emptive strong cathartics, non-narcotic adjunctive analgesic options and limited IV opioids, brief duration of transurethral drainage, and short duration of parenteral therapy and inpatient medication monitoring needed.

Several studies of surgical patients undergoing colorectal and gastrointestinal surgery have demonstrated success with early resumption of enteral nutrition leading to earlier resolution of postoperative ileus and decreased length of stay.[21-24] We found that KTX patients can drink immediately after recovery from anesthesia and shortly thereafter be advanced to a regular diet as tolerated. Our regimen allows patients to pace themselves with regard to the quantity of oral intake. Although the rate of emesis in our analysis was somewhat higher in patients within the ERAS pathway compared to historic controls (15.8% vs. 8.4%, respectively), most patients were allowed to self-limit oral intake along with the

use of IV anti-emetics and only one patient (ERAS group) was treated with nasogastric tube decompression. Additionally, readmission due to ileus or bowel obstruction was uncommon in both groups. This combined strategy appears effective and well tolerated in our patients. Others have also noted that with early oral feeding, the risk of emesis increases. This is thought to be higher especially in the absence of multimodal anti-ileus therapy. The prophylaxis and treatment of post-operative nausea and vomiting to support nutritional intake has been suggested to include: intraoperative pre-emptive antiemetics, adjunctive non-narcotic analgesics, and goal-directed IV fluid management as well as postoperative avoiding fasting; maintenance of appropriate fluid balance to support bowel movements and avoid visceral edema; avoiding the use of opioid disturbing bowel movements; avoiding anti-inflammatory treatments to reduce stress; avoiding tubes and drains; and active mobilization.

Awaiting return of bowel function remains a major barrier for discharge from both a patient and clinician perspective. An additional pre-emptive cathartic within the ERAS pathway achieved a doubling of the rate of bowel movement by the third post-operative day in the ERAS vs. HISTORIC era (61.2% vs. 31.6%). We chose castor oil due to its effectiveness as a single dose; however, others have reported that polyethylene glycol (PEG) electrolyte lavage solution administered 100 ml every hour while awake once tolerating clear liquid diet until bowel movement is effective in decreasing time to bowel movement and length of hospitalization following kidney transplantation.[25]

Other contributions toward bowel function recovery within our patients may include decreased reliance on intravenous opiates. Intravenous opiates within 24 hours post-transplant were successfully discontinued in 61.2% of ERAS and 29.5% of HISTORIC patients, yet peak and mean pain levels on post-operative day 2 were similar between the groups; suggesting that intravenous narcotics are commonly administered in situations when an oral agent would suffice. Others strategies recommended to decrease opioid consumption included pre- and post-operative gabapentin, intraoperative surgeon-delivered

TAP block with long-acting liposomal bupivacaine, use of diazepam in conjunction with narcotics, and postoperative use of acetaminophen, and nonsteroidal agents. We believe that the muscle-splitting incision utilized for kidney transplant access to the iliac fossa is a well tolerated incision with minimal associated pain and that the majority of pain that kidney transplant patients suffer is related to bloating and constipation. The basis of our analgesic regimen was to reduce the side effects of narcotics by appropriately minimizing its use.

A brief duration of transurethral drainage is desirable because increasing duration is associated with increasing risk of urinary tract infection (UTI)[26] and failure to mobilize[27]. In a recent randomized trial of early (day 1, n = 105) versus standard (approximately day 4, n = 110) removal of the transurethral catheter in patients having major abdominal and thoracic surgery, the prevalence of UTI significantly reduced with early removal (2% versus 14%).[26] In our analysis, Foley catheter removal by POD 2 occurred within 59% of patients in the ERAS era and 1.1% in the HISTORIC era, yet the incidence of urologic complications was similar. Post-kidney transplant Foley catheter removal within one or two days, has been shown to be safe in previous reports.[25,28,29]

Reduction in KTX hospital stays over time have previously been attributed to changes in the duration of parenteral therapy and inpatient medication monitoring needed.[19] We implemented reduced duration between induction therapy doses and earlier calcineurin inhibitor initiation to prepare patients for discharge readiness. The prescribing information for rATG (in treating kidney rejection) recommends administering small doses at 1- or 2-day intervals. According to the 2008 US Renal Data System annual report, rabbit antithymocyte globulin was typically given daily for 5 to 7 doses.[30] However, larger doses have been seen to confer more comprehensive lymphocyte depletion in primates[31] and, in humans, even large single doses of rATG as induction therapy has been found to be noninferior to divided-dose administration.[32] Early achievement of acceptable calcineurin levels likely promotes reduced LOS. Centers that use a full dose of calcineurin inhibitors immediately after transplant rather than delaying until the onset of allograft function may

have longer lengths of stay.[33] Therefore we administered oral immunosuppressive medications at the next available dose, either 0600 or 1800. This early dosing strategy was reflected by a greater proportion of ERAS era tacrolimus C0 levels within acceptable range relative to HISTORIC patients; however, an unintended consequence was that the target tacrolimus C0 were often higher in ERAS patients than those currently recommended, notwithstanding that the optimal C0 ranges for preventing rejection are not defined.[34,35] The rationale for aiming for high early levels was based on the assumption that tacrolimus underexposure in the first days after transplantation increases the risk of acute cellular rejection;[36] however, overexposure would foster chronic nephrotoxicity.[37] Although, these hypotheses have never been formally validated, prolonged delayed graft function is a known complication of calcineurin inhibitor use and our practice may have failed to mitigate kidney slow function amongst our cases which were already vulnerable to prolonged delayed function for other reasons.

Although fast-track or ERAS protocols are likely to be associated with a significant cost saving (due to shorter inpatient hospital stay),[38] one of the primary drivers for the implementation of our own protocol was a belief that it would offer an improved patient experience (when compared to prolonged hospital stay). Measuring patients' experiences with ERAS, however, has not been investigated very thoroughly. This is mostly due to the lack of reliable and valid tools that can be used widely across many centers to report patients' experiences. Nevertheless, in the literature on this subject, ERAS does not seem to adversely influence quality of life (QoL),[39] satisfaction[40] or psychomotor functions such as sleep quality, pain and fatigue levels after surgery.[39]

We believe an ERAS pathway can be instituted from the conception of a kidney transplant for all patients, not just those deemed to be low risk. According to our results, every patient can be treated by ERAS program, although not every patient will be fit for early discharge. Readmissions appeared in less than 7 days of discharge amongst 10.1% of ERAS and 14.7% of HISTORIC suggesting that some readmissions may have been

prevented by a longer LOS, but a lack of adverse association with ERAS. Effective implementation of ERAS is difficult. Implementation of all fast-track elements is challenging as it mandates a multidisciplinary collaboration between surgeons, nephrologists, and ancillary staff; a high rate of protocol compliance; and a good organizational structure. However, utilization of pre-specified full order sets is helpful. Secondly, we emphasize the importance of pre- and postoperative management of patients' expectations and staff motivation to prepare the patient. Scant attention is paid to this aspect of surgical care in the literature, but we maintain it is vital to the success of an ERAS program.

Our study is limited by its design as a retrospective, single center cohort analysis. It demonstrates only an association between implementation of a clinical care pathway and length of stay, not cause and effect. In addition, the care pathway changes occurred concurrently with a change in nephrology, surgeon, and transplant program leadership that may have affected length of stay. Nevertheless, sub analysis examining LOS of the transplant surgeon who remained at our facility throughout the two eras also revealed a reduction of length of stay from 5.85 days (n=34) to 4.77 days (n=57), suggesting that LOS changes occurred due to system changes rather than the practitioner specific threshold bias. Two nurse practitioners were hired to provide inpatient care, 4- and 9- months after starting the ERAS protocol to compensate for increased volume; however, the impact of these resources towards ERAS efficiency was not examined. Another untested confounder is the use of routine drainage. Routine drainage was discouraged during the ERAS era because it is an unsupported intervention that probably impairs mobilization. Ascertainment of readmission was limited to the transplant hospital; we were not able to determine if patients were admitted elsewhere; however, our strict follow-up makes this unlikely. Generalizability is limited. Regional differences may exist due to different practices, different patient populations, and different distances of patients to the transplant center. Lastly, the decision to readmit a patient is subjective and triggers for readmission may vary by physician and institution, the surgeon (LKK) may have been involved in the care of the patients at the time

of transplant or readmission and this may add potential bias to the analysis. We did not analyze the impact of our ERAS program on costs and few studies have addressed this matter properly. A recent review concluded that ERAS protocols appear to be both clinically efficacious and cost effective, but studies reporting out-of-hospital cost data are lacking. Further research is required to determine how to best evaluate costs relating to ERAS pathways while taking quality of life data into account.[41] Although long-term morbidity (more than 30 days) after KTX is important, it is unlikely that the LOS will have any impact on long-term (more than 30 days) morbidity or readmissions beyond 7 days. Our results (data not previously shown) support this. All-cause graft failures occurring between 1 - 6 months were 1/49 (2.0%), 4/69 (5.8%) and 4/116 (3.4%) when stratified by LOS ≤ 3, LOS=4, and LOS≥5, respectively, suggesting an absence of dose-dependent effect of LOS at longer-term follow-up. It has been questioned whether all ERAS elements are of equal importance and which are the key factors that determine short-term clinical outcome in the fast-track setting. Our study was not constructed methodologically to appropriately examine this issue.

We found that use of an ERAS pathway in kidney transplant recipients offer clinicians a safe and reliable care matrix to guide perioperative care. The components of our regimen has shown feasibility and efficacy in our practice, but could be amended to include or exclude other components and address different practice patterns or preferences. These results may lay the foundation for improvements in kidney transplant care by demonstrating that length of stay reduction is possible, despite higher delayed graft function rates, without compromising short term graft function or readmission rates. In the context of economic constraints with the use of marginal kidneys, we believe that our ERAS pathway is a critical aspect of comprehensive care that allows our center to provide optimal access to transplantation.

Table 1: Summary of Differences between ERAS Pathway and HISTORIC protocol for Kidney Transplant Patients

Table 2. Enhanced Recovery Pathway Metrics

Table 3: Comparison of Patient Characteristics by Era

Table 4: Comparison of Patient Outcomes by Era

ENDNOTES

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Table 1: Summary of Differences between ERAS Pathway and HISTORIC protocol for Kidney Transplant Patients

Variable	Enhanced Recovery After Surgery	HISTORIC
Preoperative patient education	Written materials and transplant evaluations/ seminars state expected LOS of 3-5 days	Written materials and transplant evaluations seminars state expected LOS of 5-7 days
Central Venous Monitoring	Place if clinically indicated due to comorbidities or for venous access	Universal placement
Extubation	Extubation in operating room if stable	Extubation in intensive care unit if deemed preferable by MD
Antithymocyte globulin	1.5 mg/kg dose daily, peripheral route, and administration q A.M regardless of prior dose completion time, total dose 3-4.5mg/kg depending on pre-transplant risk stratification.	1 mg/kg dose daily, central route, and administration only if ≥ 24 hours after prior dose completion, total dose variable depending on pre- and post-transplant (e.g. DGF, drug levels) factors
Basiliximab	20 mg at surgery and post-transplant day 1	20 mg at surgery and post-transplant day 4
Pain Management	PRN IV Hydromorphone automatic stop at 24 hours post-transplant[1,2]	PRN IV Hydromorphone until discharge[1]
Nutrition	Solid food diet started POD 1[1]	MD driven diet advancement
Foley Catheter	Removal by POD 2	Variable removal time
Intestinal Management	Daily docusate and senna PO*; Castor Oil POD 1[1]	Daily docusate PO[1]
Tacrolimus	Initiation of Tacrolimus at next dose[1]	MD driven initiation of Tacrolimus
Tacrolimus level	Target level same for all patients	MD driven target level depending of graft function
Activity	Activity advancement POD 1 [1]	MD driven initiation activity orders
Post-KTX dialysis	Performed on-site for 3-4 weeks[2]	Performed at initial dialysis center
Infusion Center	Increased utilization of infusion centers for intravenous drug administration [2]	Low utilization of infusion centers for intravenous drug administration

KTX, kidney transplant; PO, per oral; POD, post operative day; LOS, length of stay; DGF, delayed graft function

[1]indicates computerized physician order entry automatically checked order components

[2] Added within the third month after implementation of ERAS pathway

Table 2. Enhanced Recovery Pathway Metrics

Enhanced Recovery Pathway Metrics	ERAS 7/15-7/16 N=139	HISTORIC 1/14-7/15 N=95	p-value
Antithymocyte globulin administered within 2 days (administer q am vs. administer at between dose duration of 24 h)	101 (72.7)	13 (13.7)	<0.0001
Absence of intravenous narcotic beyond 24 hours (automatic CPOE vs. nurse driven)	85 (61.2)	28 (29.5)	<0.0001
Solid food order by post-operative day 1 (automatic CPOE vs. MD driven)	119 (85.6)	7 (7.4)	<0.0001
Foley removal within 2 days	82 (59.0)	1 (1.1)	<0.0001
Castor Oil administered by post-operative day 2 (automatic castor oil and senekot vs. automatic senekot)	92 (66.2)	0 (0)	<0.0001
Tacrolimus C_0 level post-operative day 3 between 6-14 ug/L (automatic initiation of tacrolimus at next dose vs. MD driven)	72 (51.8)	27 (28.4)	<0.0001

Table 3: Comparison of Patient Characteristics by Era

Characteristic* N(%) or mean +/- SD	ERAS 7/15-7/16 N=139	HISTORIC 1/14-7/15 N=95	p-value
Recipient Age < 40 years	19 (13.7)	14 (14.7)	0.8180
Recipient Age 41-65 years	83 (59.7)	64 (67.4)	0.2340
Recipient Age >65 years	37 (26.6)	17 (17.9)	0.1200
Recipient, Male	78 (56.1)	58 (61.1)	0.4522
Recipient race, black	37 (26.6)	26 (27.4)	0.8990
Recipient body mass index > 35 kg/m^2	35 (25.2)	17 (17.9)	0.1881
Recipient diabetes mellitus	58 (41.7)	30 (31.6)	0.1156
Recipient, Prior Solid Organ Transplant	20 (14.4)	13 (13.7)	0.8972
Recipient, preemptive transplant	17 (12.2)	17 (17.9)	0.2272
Recipient, ureteral double J stent placement	54 (38.8)	94 (98.9)	0.0001
Recipient DR mismatch of 0 Recipient DR mismatch of 1 Recipient DR mismatch of 2	14 (10.1) 60 (43.2) 65 (46.8)	16 (16.8) 40 (42.1) 39 (41.1)	0.2943
Recipient time on dialysis: Low < 500 days Recipient time on dialysis: Medium 501-1500 days Recipient time on dialysis: High > 1500 days	36 (29.3) 67 (54.5) 20 (16.3)	19 (24.4) 38 (48.7) 21 (26.9)	0.1842
Recipient, Distance from home to transplant center, miles	14.9±16.9	16.1±21.9	0.6494
Recipient, antithymocyte globulin induction	135 (97.1)	83 (87.4)	0.0037
Recipient antithymocyte globulin total dose ≤ 3.5 mg/kg***	99 (73.3)	59 (71.1)	0.9203
Recipient, calculated panel reactive antibody level > 0%	58 (41.7)	30 (31.6)	0.1156
Recipient, delayed graft function**	58 (46.4)	21 (25.0)	0.0015
Index Hospitalization PRBC administration > 2 units	15 (10.8)	14 (14.7)	0.3864
Index Hospitalization administration of warfarin	15 (10.8)	8 (8.4)	0.5498
Index Hospitalization reoperation	9 (6.5)	2 (2.1)	0.2069
Index Hospitalization additional cathartic administered	83 (59.7)	48 (50.5)	0.1645
Donor Age < 40 years Donor Age 41-65 years	73 (52.2) 59 (42.5)	48 (50.5) 45 (47.4)	0.4468

Donor Age >65 years	7 (5.0)	2 (2.1)	
KDPI<35**	33 (26.4)	37 (44.1)	
KDPI 36-85**	73 (58.4)	38 (45.2)	0.0292
KDPI>85**	19 (15.2)	9 (10.7)	
Donor, non-local**	78 (62.4)	4 (4.7)	0.0001
Kidney Cold Ischemia Time ≥30 hours**	78 (62.4)	4 (4.7)	0.0001
Kidney Type, Living donor	14 (10.1)	11 (11.6)	0.7140
Donation after circulatory death**	40 (32.0)	26 (31.0)	0.8731

PO, per oral; DGF, delayed graft function; PRBC, packed red blood cell; Kidney Donor Profile Index (KDPI)

*Time on dialysis cut-offs were approximately at 25th and 75th percentiles, delayed graft function was defined as dialysis within 7 days of KTX, KDPI was obtained from DonorNet (portal.unos.org) at the time of offer and non-local includes regional and national shares.

**Only deceased-donor cases were included.

***Only patients receiving anti-thymocyte globulin included

Table 4: Comparison of Patient Outcomes by Era

Characteristic N(%) or mean +/- SD	ERAS 7/15-7/16 N=139	HISTORIC 1/14-7/15 N=95	p-value
Length of Stay ≤3 days Length of Stay = 4 days Length of Stay ≥5 days	45 (32.4) 39 (28.1) 55 (39.6)	4 (4.2) 30 (31.6) 61 (64.2)	<0.0001
7-day readmission to hospital	14 (10.1)	14 (14.7)	0.3833
30-day readmission to hospital	38 (27.3)	26 (27.4)	0.9203
Reason for Readmission Nausea/Vomiting/Ileus Cardiopulmonary Graft Function Infection Metabolic Surgical Other (fall, neuropathic pain, deep vein thrombosis) Non-surgical bleed	 2 (1.4) 2 (1.4) 14 (10.1) 7 (5.0) 6 (4.3) 4 (2.9) 2 (1.4) 1 (0.7)	 2 (2.1) 4 (4.2) 7 (7.4) 4 (4.2) 2 (2.1) 4 (4.2) 2 (2.1) 1 (1.1)	
30-day visit to emergency room	13 (9.4)	7 (7.4)	0.5827
30-day mortality	1 (0.71)	0(0)	NA
Clinic visits per patient within 30 days following discharge*	6.60	7.03	0.2000
Graft failure during transplant hospitalization	2 (1.4)	1 (1.0)	NA
30-day graft failure	0	0	NA
Urologic complication requiring radiologic or operative intervention within 90 days of transplantation	4 (2.9)	4 (4.2)	NA
Index Hospitalization Secondary Endpoints Bowel movement by postoperative day 3 Food PO intake during first or second post operative meal Zofran administration beyond post-operative day 2 Diarrhea Emesis Pain peak level on post-operative day 2 <7 (10 total) Pain mean level on post-operative day 2 < 5 (10 total)	 85 (61.2) 62 (44.6) 87 (62.6) 29 (20.9) 22 (15.8) 53 (38.1) 88 (63.3)	 30 (31.6) 12 (12.6) 63 (66.3) 11 (11.6) 8 (8.4) 35 (36.8) 62 (65.3)	 <0.0001 <0.0001 0.5596 0.0639 0.0961 0.8418 0.7596

SD, standard deviation; PO, per oral.

*Excludes patients that were readmitted within 30 days of discharge (ERAS n = 101 vs HISTORIC n =69)