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Enhanced Recovery After Surgery Pathway in Kidney Transplantation: The Road Less Traveled

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Background. Enhanced recovery after surgery (ERAS) pathway is a multimodal perioperative care pathway designed to achieve early recovery after surgery. ERAS protocols have not yet been well recognized in kidney transplantation. The aim of this study was to investigate the impact of ERAS pathway on early recovery and short-term clinical outcomes of kidney transplant. **Methods.** This is a single-center retrospective analysis comparing the outcomes of 20 adult kidney transplant recipients subjected to ERAS pathway with 20 adult recipients operated before ERAS with traditional standard of care. **Results.** There were no significant differences between both groups regarding age, gender, race, dialysis status, living donor percentage, cold ischemia time, and warm ischemia time. Median hospital stay for ERAS patients was 2 d. Overall median pain scores were significantly lower in the ERAS group versus non-ERAS group (morning after surgery pain score 2 versus 5; peak pain score 4.5 versus 10; lowest pain score 0 versus 2; $P=0.0001$). ERAS patients had earlier ambulation (walking) and oral nutrition (regular diet) (first versus second day postoperatively in traditional group). Earlier bowel movement was observed in ERAS patients. There were no significant differences in graft function or 30-d readmission rates between both groups. **Conclusions.** Implementation of ERAS pathway in kidney transplantation is feasible. Using ERAS is associated with less pain, earlier ambulation and advancement of oral nutrition, and short hospital stay.

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INTRODUCTION

Enhanced recovery after surgery (ERAS) protocol is a multimodal perioperative care pathways designed to promote early recovery after surgery by sustaining preoperative organ function and decreasing the stress response

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A.M.E. developed the enhanced recovery after surgery pathway, study design, literature review, data collection, data analysis, and interpretation and did of results, and writing of the article. I.G. did data analysis, interpretation results and writing of the article. A.M. did data collection, interpretation of results, and writing of the article. K.W. did data analysis, interpretation of results, and writing of the article. J.S.B. did data collection, interpretation of results, and writing of the article.

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All patient data were approved for use by the Institutional Review Board of our institute (R20190004).

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following surgery.¹ ERAS protocols have been widely recognized in general surgery, improving the quality of the recovery, increasing patient satisfaction, and decreasing the length of hospital stay.² The key components of ERAS protocols include preoperative education, nutritional optimization, opioid-sparing perioperative pain control, nausea prophylaxis, early mobilization, and oral nutrition.³⁻⁵ Use of ERAS has not gained widespread recognition in kidney transplantation. Management of renal transplant cases is complicated and standardized in many ways; however, surgical tradition usually controls practice patterns, and there is a paucity of data examining ERAS implementation in these patients.⁶ The aim of this study was to investigate the impact of the ERAS pathway on early recovery and short-term clinical outcomes of kidney transplant. We hypothesized that use of the ERAS pathway would result in faster recovery and better quality of care. The ultimate intent of this work is to open the door for the development of a model for spread, scale, and sustainability of ERAS in the kidney transplantation field.

MATERIALS AND METHODS

This is a single-center retrospective study to evaluate the effectiveness of the ERAS pathway in adult isolated kidney transplantation when compared with a historical cohort with traditional standard of care. The ERAS pathway was initiated July 2018 at our program by the surgeon (A.M.E.). We studied adult patients who were subjected to the ERAS pathway in the period between July 2018 and June 2019. Patients

with psychological or opioid dependency history (3 cases) and those who were complicated by hematoma formation (2 cases) were excluded from the study. We compared the outcomes of 20 adult kidney transplant recipients subjected to the ERAS protocol to a prior cohort of 20 consecutive adult recipients operated on before ERAS with traditional standard of care in the period between December 2017 and July 2018. All patient data were approved for use by the Institutional Review Board of our institute (R20190004).

Standard of Care Pathway

In this pathway, patients were asked to be nil per orally for 8 h before the surgery. There were no standard protocols followed by anesthesia team for intraoperative fluid management. Management was individualized on a case-by-case basis. Systolic blood pressure (SBP) >120 at the time of reperfusion was achieved using dopamine at 3–7 µg/kg/min and intravenous (IV) crystalloid boluses. Pain management included intraoperative IV opioid boluses, postoperative patient controlled analgesia morphine, or Dilaudid. Zofran was used for postoperative nausea and vomiting prophylaxis. Diet was advanced as tolerated after surgery.

ERAS Pathway

(I) Preoperative ERAS

Education

Patients received detailed education the ERAS pathway and hazards of narcotics intake, and we set up the expectations for recovery course during the preoperative clinic visit.

Diet

Clear liquids were allowed until 2 h before the start of the surgery. High carbohydrate clear drink was given, after which the 2-h fasting period started.

Analgesia

Acetaminophen 975 mg per oral (PO) was given 2 h before the surgery.

Antiemetics

Scopolamine patch was used for patients who were high risk for postoperative nausea and vomiting.

(II) Intraoperative ERAS

Diet

Patients received nil per orally and orogastric tube.

Analgesia

- Surgical site infiltration (Bupivacaine 0.5 with epinephrine 1:200 000) was performed by the surgeon before incision and at the end of surgery.
- Morphine 4 mg or acetaminophen 1 g IV was administered toward the end of the case.

Antiemetics

Patients received Zofran 4 mg IV when closing.

Fluid management

- A goal-directed fluid therapy (GDFT) was done with crystalloid infusion at 3–5 mL/kg/h supplemented with albumin 5% if needed.

- Fluid management was guided by measuring the stroke volume and stroke volume variation using a noninvasive monitor of cardiac output.

Diuretics

After reperfusion, 100 mg of Furosemide IV push (1–2 times) was administered. Then, 500 mg of chlorothiazide was administered (to induce an aggressive diuresis, reduce oxygen requirement of kidney, and help minimize reperfusion injury).

Blood pressure

The goal is to keep SBP >120 at the time of reperfusion, with dopamine starting at 3–7 µg/kg/min and albumin 5% if needed.

(III) Postoperative ERAS

Diet

Early diet was resumed once patient is awake and advance as tolerated.

Analgesia

Acetaminophen PO 325 mg 1–2 tab Q 4H pro re nata (as needed) was administered without exceeding daily maximum dose.

Morphine 1 mg 1-time dose is allowed for breakthrough pain.

Antiemetics

Zofran 4 mg PO Q 6H pro re nata (as needed) was administered.

Blood pressure

The goal is to keep SBP >120 and mean arterial pressure >70, with dopamine at 3–7 µg/kg/min and albumin 5% if needed.

Ambulation

Early ambulation was encouraged (out of bed to chair 4 h after surgery, and then walking 3 times in first day postoperatively).

Medications

Famotidine 20 mg was administered before breakfast, and Docusate Sodium 100 mg was administered twice a day after meals.

ERAS Perioperative Analgesia

One of the key components of a successful ERAS program is the implementation of optimal perioperative analgesia to enhance bowel recovery, ambulation, and rehabilitation. An ideal multimodal analgesic technique would include surgical site infiltration combined with perioperative acetaminophen. Surgical site infiltration was done using bupivacaine 0.5 with epinephrine 1:200 000. Combining previously used local anesthetic techniques in 1 comprehensive novel protocol was done.

Surgical Site Infiltration Before Incision (Pre-emptive Analgesia)

Pre-emptive analgesia concept is based on the hypothesis that the most effective way to decrease postsurgical pain is to inhibit nociceptive input from afferent stimuli to the central nervous system preventing central nervous system hyperexcitability and sensitization of pain.⁷⁻¹⁰

Ilioinguinal-iliohypogastric Nerve Block Before Incision

The needle was inserted at the point between the medial three-fourth and the lateral one-fourth of the line drawn

between the umbilicus and the anterior superior iliac spine. Needle insertion was done at a 45° to 60° angle directed toward the midpoint of the inguinal ligament, until the external oblique muscle was pierced with a “click” (below the fascia of the external oblique muscle by loss of resistance method), and then, after an aspiration test for blood, we injected 4 mL of Bupivacaine 0.5 with epinephrine 1:200 000.^{11,12}

Surgical Site Infiltration at the End of the Surgery

Based on neuroanatomy, our surgical site infiltration consisted of administration of local anesthetic into subfascial, subcutaneous, and subdermal tissue planes (to block the peripheral nerve endings). The needle was inserted approximately 1 to 2 cm into the tissue plane, and local anesthetic was injected while slowly withdrawing the needle, reducing the risk of intravascular injection.¹³

ERAS in Deceased Donor Kidney Transplant Cases

We followed same protocol with paying attention to certain areas. Typically, we asked our potential candidate to hold solid diet 6–8 h before the potential time of the surgery. Clear liquids were allowed till 2 h before the start of the surgery when high carbohydrate clear drink was given at the time of the admission, after which the 2-h fasting period started. Given that education was not done in preoperative clinic visit, we dedicated more time to education when patient arrived to the hospital for transplantation. It is very important to run immediate laboratory investigations for the patient on arrival to see if the patient needs any dialysis before starting surgery.

ERAS Discharge

ERAS patients were discharged home postoperatively day 2 on Acetaminophen for pain control and Oxycodone/Acetaminophen (5/325 mg) for severe pain not controlled by Acetaminophen. They were instructed to take Docusate Sodium 100 mg twice a day after meal as needed. They were encouraged to continue ambulation and using incentive spirometer. Patients were discharged with the foley catheters that were removed in the clinic. If more parental immunosuppression doses were needed, they were given in our infusion center when patients come for their clinic follow-up. Typically, kidney transplant recipients were seen in clinic twice a week early after transplant. If patients were living far from the hospital and were not able to afford staying locally, we arranged their accommodation in our hospital lodge for patients' families.

Data Management

A prospective database is maintained with much of the perioperative details and clinically relevant endpoints. Recipient demographics, operative details, postoperative course, and operative complications were reviewed. Pain was assessed using a 0–10 verbal response scale. The morning after surgery pain score was recorded between 8 and 9 AM. The highest and the lowest pain scores in the whole admission were recorded.

Statistical Analysis

Continuous variables were expressed as mean (\pm SD) and compared by using the *t* test or expressed as median (range) and compared by using Mann-Whitney *U* test depending on whether they were normally distributed or not. Categorical variables were expressed as percentages and compared using the Chi-square test. A *P* < 0.05 was considered significant. All statistical calculations

were done by the computer program SPSS (Statistical Package for the Social Science) version 20 for Microsoft windows.

RESULTS

The outcomes of 20 adult isolated renal transplant recipients subjected to the ERAS protocol were compared with 20 matched recipients operated before ERAS with traditional standard of care. There were no statistically significant differences between both groups regarding age, gender, race, body mass index, history of diabetes, history of hypertension, dialysis status, living donor percentage, cold ischemia time, warm ischemia time, and operative time (Table 1).

Postoperative Course

Median hospital stay for ERAS patients was 2 d (Table 2). There was no significant difference in graft function in both groups. There were no significant differences in urine production or creatinine drop in the first 24 h between both groups. Overall pain scores were significantly lower in the ERAS group. ERAS patients had significantly earlier ambulation and toleration of regular diet compared with the non-ERAS group. All ERAS patients had 4-h bed rest versus 24-h bed rest in the other group. ERAS patients were fully ambulating in the first versus second day postoperatively in the traditional group. Toleration of regular diet occurred significantly earlier in the ERAS group (in the first versus second day postoperatively in the traditional group). Earlier bowel movement was observed in ERAS patients. Thirty-day readmission happened only in 1 of the ERAS patients because of upper gastrointestinal bleeding that required endoscopic management and blood transfusion.

DISCUSSION

The ERAS pathway has not yet been well recognized in kidney transplant field as in general surgery. Recently, there were some published studies on the feasibility of the ERAS protocol in live kidney donors^{14,15} and kidney transplant recipients.^{6,16} The goal of ERAS protocols is to improve the perioperative patient journey. We sought to share our experience of transforming our kidney transplant program from a non-ERAS into an ERAS program.

TABLE 1.
Recipients baseline characteristics

	Post-ERAS	Pre-ERAS	<i>P</i>
Age	56.9 \pm 14.02	52.1 \pm 14.03	0.286
Gender (Male:female)	11 (55%):9 (45%)	13 (75%):7 (35%)	0.519
Race (White:African American)	15 (75%):5 (25%)	14 (70%):6 (30%)	0.723
BMI	31.358 \pm 5.124	30.517 \pm 4.980	0.616
History of hypertension	19 (95%)	19 (95%)	1.000
History of diabetes	6 (30%)	5 (25%)	0.723
RRT	15 (75%)	14 (70%)	0.782
Living donor kidney transplant	5 (25%)	7 (35%)	0.311
CIT (in min)	986.500 (50–1679)	608.500 (41–1851)	0.188
WIT (in min)	30.471 \pm 8.719	27.790 \pm 6.973	0.320
Operative time (in min)	172 (125–324)	177 (134–235)	0.964

BMI, body mass index; CIT, cold ischemia time; ERAS, enhanced recovery after surgery; RRT, renal replacement therapy; WIT, warm ischemia time.

TABLE 2.
Postoperative course and outcomes

	Post-ERAS	Pre-ERAS	P
Urine (first 24h) ml	6117.5 (1255–13199)	5225 (1280–12300)	0.387
Preoperative creatinine	8.255 (3.67–18.12)	6.745 (3.32–21.22)	0.449
POD 1 creatinine	5.725 (2.51–15.3)	5.580 (1.72–18)	0.745
POD 30 creatinine	1.195 (0.75–2)	1.435 (0.75–3.81)	0.066
IV narcotics in hospital	No	Yes: PCA (POD 1)	
Median morning after surgery pain score	2 (0–4)	5 (2–10)	0.0001
Median peak pain score	4.5 (1–7)	10 (6–10)	0.0001
Median lowest pain score	0	2 (0–4)	0.0001
Activity	DOS: Up in chair 4h postsurgery POD 1: Up walking 3 times POD 2: Up walking 4 times	DOS: Bedrest 24 h POD 1: Up in chair POD 2: Up walking 2 times POD 3: Up walking 4 times	
Diet	Day of surgery: advanced to full liquid diet POD 1: advanced to regular diet for the breakfast.	Day of surgery: ice chips POD 1: clear liquid diet for breakfast and advance to full liquids POD 2: advance to regular diet	
Nausea or vomiting	0%	75%	0.001
Passing flatus: median POD	1	2 (1–3)	0.0001
First BM: median POD	2 (2–4)	4 (3–6)	0.001
30-d readmission	1 (5%)	0	0.311
Used narcotics after discharge (percocet 5/325 mg) doses	0.5 (0–3)	20 (16–24)	0.0001

Bold variables are those with significant *P* value.

DOS, day of surgery; ERAS, enhanced recovery after surgery; PCA, patient controlled analgesia; POD, postoperatively day.

Factors that delay discharge of a kidney transplant recipient from the hospital after an uncomplicated transplant include needed parenteral analgesia, intravenous fluids, parenteral immunosuppression, bed rest, and patient and medical team expectation.^{16,17} Although data around ERAS in kidney transplantation is sparse, our data show shorter hospital stay (2 d) than previously published studies about ERAS in kidney transplant. Espino et al⁶ described that the median length of stay was 4 d among ERAS patients. Dias et al¹⁶ reported that the median length of stay for patients on the ERAS protocol was 5 d.

Postoperative opioids have many hazards that were explained in detail to our patients. Hazards include delayed bowel motility, dizziness, blurry vision, delayed ambulation, impairment of gut barrier integrity (allowing bacteria translocation into the peritoneal cavity and blood),^{18,19} modulation of multiple immune pathways responsible for host defense against pathogens increasing the risk of infection,^{20,21} and change of the microbiota composition, leading to increased susceptibility to various pathogens and impaired mucosal immune responses.²²

In contrast to other classical ERAS protocols, some issues need to be addressed differently in kidney transplant. For example, pain control cannot be done using nonsteroidal anti-inflammatory medications because of their nephrotoxicity.²³ Our ERAS pathway is based on multimodal perioperative pain-control techniques, of which local anesthetics are a cornerstone. We used Bupivacaine 0.5 with epinephrine 1:200 000 for surgical infiltration. Combining previously used local anesthetic techniques^{7–13} in 1 comprehensive novel protocol was done. It included preincision surgical site infiltration, preincision nerve block, and surgical site infiltration at the end of the surgery.

Of the major elements adopted by ERAS to facilitate recovery, consumption of preoperative carbohydrate-rich clear

liquids and reduction of preoperative fasting have provided important benefits. Traditional preoperative fasting does not necessarily decrease gastric secretion or increase the gastric pH, and, hence, we followed the American Society of Anesthesiologists' guidelines allowing clear liquids until 2 h before the anesthesia induction.²⁴ This increases patient comfort by decreasing presurgical thirst, hunger, and anxiety without increasing pulmonary aspiration risk.²⁵ Typically, renal transplant patients have prolonged fasting and dehydration (because of preoperative dialysis) in preparation for transplantation.¹⁶ Carbohydrate-rich clear liquids have been reported to decrease insulin resistance and patient catabolism, helping perioperative glucose control and muscle preservation.^{26–28}

GDFT is an important element of the ERAS pathway. It is important to realize that central venous pressure measurement is not an accurate or reliable marker of the volume status in most cases.^{29,30} Several studies have shown that intraoperative GDFT guided by measuring the stroke volume and stroke volume variation using a noninvasive cardiac output monitor can decrease complications of major surgery by 25%–50%.^{31–33} It is essential to avoid excessive fluid administration that may lead to weight gain, bowel wall edema, prolonged ileus, and delayed discharge.^{34,35} Fluid overload increases the risk for cardiovascular complications in kidney transplant recipients.^{36,37}

There were no emesis episodes in our ERAS group, whereas Espino et al reported that the rate of emesis in their study was somewhat higher in patients subjected to ERAS pathway compared with historic cohort (15.8% versus 8.4%, respectively).⁶ The prophylaxis and treatment of postoperative nausea and vomiting to support nutritional intake have been considered in our protocol to include intraoperative pre-emptive antiemetics, non-narcotic analgesics, optimization of fluid balance, and early postoperative oral nutrition.

Reduction in kidney transplant hospital stay has previously been attributed to changes in the duration of needed parenteral therapy and inpatient medications.³⁸ We applied some strategies to minimize the need of staying in the hospital. Patient could be discharged with Foley catheter to be removed in first clinic visit. Completion doses of immunosuppression medication could be given during clinic follow-up visits if needed. Remote residence of the patients could be an obstacle. We overcame it by providing lodging to those who cannot afford staying locally. We think that patient recovers faster after leaving the hospital and going back to their home or a home-like atmosphere. Additionally, we think that this may help in reducing the risk of acquiring nosocomial infection in these immunosuppressed patients.

Although ERAS pathways are likely to be linked with significant cost savings from a reduction in hospital stay,³⁹ the main drive for the implementation of our ERAS pathway was a belief that it would improve our patients' experience and recovery. We considered it a quality rather than cost matrix. ERAS pathways have been reported to be both clinically and cost effective. Further studies are needed to determine how to best investigate cost saving related to the ERAS pathway while taking quality of life data into consideration.⁴⁰

Despite the obvious body of evidence showing that ERAS pathways lead to better outcomes, they are still facing a challenge with traditional surgical doctrine, and as a result, their use has not been widespread.^{41,42} Although clinical decision making and experience are considered essential for successful outcomes, we believe that more protocolized care pathways can enhance recovery without increasing complications.

We outline the basic strategies we used to energize ERAS pathways and to reach these outcomes:

- Building a comprehensive written protocol, strict adherence to its key components, regular internally auditing, and utilization of prespecified full-order sets are essential to achieve success.
- ERAS should be presented as a multidisciplinary perioperative care pathway designed to facilitate early recovery.
- Integration of coordinators, social workers, dietitians, pharmacists, executive leaders, and anesthesia team to optimize the protocol in the best way feasible in each program.
- Detailed education of nursing staff about ERAS protocol.
- Patients' education about the recovery pathway and the dynamics behind each change in the care and expected goals.
- The success in the first case was the motive for the whole team to buy in the ERAS pathway.

We believe that education and setting up the expectations of the enhanced recovery are the vital key to reach better outcomes. Early in the process of ERAS implementation, we noticed that there is tendency of some medical care personnel to follow the traditional pathway. Therefore, careful and detailed monitoring of every care step, continuous education, and solving any logistical problems are significantly needed for the success of the ERAS pathway. While switching to the ERAS program, it is not enough to gather the team in the conference room and educate them about the ERAS pathway. Additionally, it is mandatory to extend education and guidance processes through availability of certain physicians/educators in every care phase.

Espino et al emphasized the significance of pre- and postoperative management of patients' expectations and staff enthusiasm to prepare the patient.⁶ Little attention was paid to this aspect of surgical care in the literature, but we believe that it is essential for the success of an ERAS program. Further studies are needed to investigate the importance of this component of the ERAS pathway. The implementation of ERAS pathways in renal transplant patients may offer a reliable care matrix to guide perioperative care. Our ERAS pathway has shown applicability and efficacy in our practice but could be modified to include or exclude other components based on different patterns of practice. Our results may lay the base for refinements in renal transplant care.

Our study is limited by its design as a retrospective, single-center cohort analysis of a small number of patients; however, the sample number was enough to show the significant differences between both groups. Our study did not address whether all ERAS components are of equal significance or which are the key components to determine clinical outcomes. Cost impact analysis and measuring patients' satisfaction with ERAS were not performed in our study. Regional differences may exist because of different practice patterns, patient populations, and distances of patients to the transplant hospital.

CONCLUSION

Application of the ERAS pathway in kidney transplantation is feasible with some modifications to adapt unique dynamics of transplantation. Using ERAS is associated with improved pain scores, earlier ambulation and advancement to regular diet, and short hospital stay. Transforming a non-ERAS program into an ERAS program should be approached as a multidisciplinary kind of care.

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