Use of Polyethylene Glycol Electrolyte Solution Expedites Return of Bowel Function and Facilitates Early Discharge after Kidney Transplantation

Eric Treat, MD, FACS, Avi Baskin, MPhil, Andy Lin, BS, Nicole Cohen, NP, Corinne Del Rosario, NP, Hans Albin Gritsch, MD, FACS

BACKGROUND: Delay in the return of bowel function often prolongs hospitalization after kidney transplantation, leading to increased patient morbidity and health care costs. Polyethylene glycol (PEG) solution has been observed to aid the return of bowel function in postoperative patients undergoing abdominal surgery.

STUDY DESIGN: Using a 2-arm, single-surgeon, nonrandomized study, we compared the addition of PEG along with early resumption of diet with a control group using only early resumption of diet in kidney transplantation patients.

RESULTS: There were 51 subjects in the control group and 47 subjects in the PEG intervention group. The primary outcomes measure, time to bowel movement, was significantly shorter than the control group by an entire day (2.9 $\pm$ 1.1 days vs 4.0 $\pm$ 1.3 days; $p < 0.001$). In propensity score analysis, patients receiving PEG had bowel movements sooner (-1.06 ± 0.25 days; $p < 0.001$) and decreased lengths of stay (-1.16 ± 0.27 days; $p < 0.001$).

CONCLUSIONS: Polyethylene glycol significantly reduced time to return of bowel function and postoperative length of stay. By adding PEG to the postoperative protocol, we can help to reduce costs of hospitalization and improve overall outcomes in renal transplantation patients. (J Am Coll Surg 2016;222:798–804. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

In the United States, more than 29,000 patients with end-stage renal disease underwent kidney transplantation in 2014.[1] These patients require postoperative hospital admission for recuperation, which incurs additional expense to the overall transplantation procedure cost. Hospital lengths of stay after kidney transplantation have decreased to a mean of 7 days, however, mean daily costs of hospitalization have risen substantially.[2] Therefore, continued development of safe and effective innovations in postoperative care to minimize length of hospitalizations are needed to reduce the overall burden of transplantation to the health care system.

A major determinant of length of stay is postoperative return of normal bowel function. Multiple randomized controlled studies involving nontransplantation abdominal surgery patients have demonstrated improved return of early bowel function and decreased lengths of hospitalization using different strategies, such as early refeeding (within 24 hours), chewing gum, and bisacodyl administration.[3-6] In one retrospective study, patients given polyethylene glycol (PEG) within 48 hours after open partial colectomy were found to have significantly decreased times to first bowel movement and hospital stay when compared with patients who did not receive this intervention.[7] To our knowledge, no studies in kidney transplantation have directly assessed strategies for expediting return of bowel function and shortening length of hospitalization.

Disclosure Information: Nothing to disclose.

Support: Supported in part by National Institutes of Health Training Grant T32-DK-07789 for Dr Treat.

Presented at the Urologic Society for Transplantation and Renal Surgery, New Orleans, LA, May 2015.

Received December 17, 2015; Revised January 29, 2016; Accepted January 30, 2016.

From the Department of Urology, David Geffen School of Medicine at UCLA (Treat, Baskin, Cohen, Del Rosario, Gritsch) and The Institute for Digital Research and Education Statistical Consulting Group, University of California-Los Angeles (Lin), Los Angeles, CA.

Correspondence address: Avi Baskin, MPhil, Department of Urology, David Geffen School of Medicine at UCLA, 10945 Le Conte Ave, PVUB 3361, Los Angeles, CA 90095-7309. email: ABaskin@mednet.ucla.edu

© 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.

http://dx.doi.org/10.1016/j.jamcollsurg.2016.01.058
ISSN 1072-7515/16

This study aims to measure the impact of using PEG solution on postoperative kidney transplantation recovery. In particular, we hypothesize that early postoperative use of PEG in kidney transplant recipients will decrease the time to first bowel movement and the overall length of the transplantation hospitalization. Additional outcomes will also be assessed, including patient-reported pain scores, opioid analgesic use, graft function, surgical and medical complications, and readmission rates.

METHODS

Study population

All patients with end-stage renal disease older than the age of 18 years undergoing renal transplantation (living and deceased donors) at a single academic referral center by a single surgeon (HG) were eligible for this study. Only multi-organ transplant recipients were excluded. The routine postoperative protocol for resuming diet was modified with the addition of PEG on a specific day in October 2013. Therefore, the control cohort included all eligible consecutive patients undergoing transplantation before October 2013 and the PEG treatment cohort included all eligible consecutive patients undergoing transplantation after October 2013. Outcomes measures were analyzed with an intention to treat design. The sample size for each cohort was estimated a priori by the difference between 2 independent means for time to first bowel movement, as a 2-tailed test, with an effect size of 0.5, α of 0.05, and power of 0.8, allocated 1/1. Approximately 64 subjects in each group were estimated. In post hoc, the achieved power was 0.99 ($1 - \beta$ error probability) having an effect size of 0.89 using the sample sizes reported here. This study was approved by the IRB (IRB#14-000231) and conducted following the principals set forth in the Declaration of Helsinki.

Intervention

The standard of care protocol for advancing the diet for control cohort patients was as follows: npo postoperative day 0; clear liquid diet (as tolerated) postoperative day 0 to 1; then advanced to a regular diet per the patient's discretion. The same protocol was used for the PEG treatment cohort. Additionally, they were given 100 mL PEG (sulfate-free polyethylene glycol electrolyte lavage solution, GoLytely, pineapple flavor; Braintree Laboratories, Inc.) every hour when awake and once started on a clear liquid diet. This was continued until they achieved a bowel movement. They also were advanced to a regular diet per their discretion as tolerated, irrespective of having had a bowel movement.

Data collection and outcome measures

Patient demographics and characteristics were collected from the institutional electronic medical records. Cause of end-stage renal disease and number of days on dialysis (date starting dialysis minus date of surgery) were recorded as reported to the United Network for Organ Sharing for transplant listing. The length of surgery was calculated from the time of intubation to extubation. Body mass index was measured on the day of transplantation. Estimates of blood loss, peritoneal violation during surgery, and intraoperative complications were noted as recorded by the surgeon. Induction immunosuppression medications and intraoperative transfusions were noted from anesthesia records. The time to first ambulation, flatus, bowel movement, clear diet, and regular diet where measured from the time of extubation. Pain scores were patient reported using the 0 to 10 visual analog scale and recorded by the bedside nurse per standard of care protocol. Narcotic patient-controlled analgesia was used until transition to oral pain medication. Administered medications were retrieved from the medicine administration record. Morphine equivalents were calculated by using standard conversions.[8] Length of hospitalization was measured as date and time of extubation to date and time of discharge. Rejection episodes were defined by biopsy findings according to the most recent Banff criteria for rejection, and subsequently requiring medical treatment within the first 30 days postoperatively.[9] Functioning grafts were defined by the patient's need for dialysis at postoperative day 30. Delayed graft function was defined as need for dialysis within the first postoperative week. Postoperative complications were defined as any deviation from routine postoperative care during the transplantation admission (see full list of complications in Table 1). Reasons for readmission were the presenting diagnosis that prompted admission to the hospital after discharge. The primary outcomes measure was time to first bowel movement. Secondary outcomes included length of hospitalization, patient-reported pain, total opioid analgesic use, postoperative complications, and readmission rates.

Statistical analysis

Basic descriptive statistics were performed using Welch 2-sample *t*-test, Wilcoxon signed rank test, chi-square test, and Fisher's exact test. Data were analyzed for normalization and log conversion was used in variables to achieve normal distribution. Significance was determined at the $p < 0.05$ level. Time to bowel movement and length of stay were estimated in PEG and control groups by the Kaplan-Meier estimator. Additionally, propensity score analysis was performed to adjust estimation of a causal treatment effect for confounding between treatment

Table 1. Postoperative Outcomes

Variable	Polyethylene glycol group (n = 47)	Control group (n = 51)	p Value
Days to first flatus, mean (SD)	2.4 (1.0)	2.2 (1.1)	0.303
Days to first bowel movement, mean (SD)	2.9 (1.1)	4.0 (1.3)	<0.001
Days to first ambulation, mean (SD)	1.7 (1.1)	1.4 (1.3)	0.011*
Days to starting clear liquids, mean (SD)	0.8 (0.2)	1.0 (0.5)	0.007
Days to starting regular diet, mean (SD)	1.5 (0.4)	2.2 (0.8)	<0.001
Length of hospitalization, d, mean (SD)	5.6 (2.9)	6.7 (4.4)	0.042*
Readmit within 30 d of discharge, n (%)	5 (10.6)	14 (27.5)	0.065
Functioning graft at 30 d, n (%)	46 (97.9)	49 (96.1)	1
Rejection episodes within 30 d, n (%)	1 (2.1)	0 (0)	0.480†
Serum creatinine POD 4, mean (SD)	3.94 (4.07)	3.76 (3.25)	0.81
Serum creatinine POD 30, mean (SD)	1.74 (1.19)	1.60 (0.92)	0.525
Reasons for readmission, n (%)			
Subjects without readmission	42 (89)	37 (72)	
Allograft biopsy	0	2	
Fever	0	2	
Diarrhea	1	1	
Hyperkalemia	1	1	
Atrial fibrillation with rapid ventricular rate	0	1	
Hematoma requiring evacuation	0	1	
Hyperglycemia	0	1	
Nausea and vomiting	0	1	
Perinephric fluid collection	0	1	
Upper-extremity deep vein thrombosis	0	1	
UTI	0	1	
Venous access removal	0	1	
Acute kidney infection	1	0	
Fluid overload	1	0	
Shortness of breath	1	0	
Postoperative complication, n (%)			
Subjects without complication	37 (79)	34 (67)	
Delayed graft function	9	13	
Atrial fibrillation	0	1	
Non ST-segment elevation MI	0	1	
Ileus	0	1	
Pyelonephritis	0	1	
UTI	0	1	
Allograft nephrectomy	1	0	

*Log converted value used for normalized distribution.
†Fisher's exact test.
POD, postoperative day; UTI, urinary tract infection.

assignment and subject characteristics. Inverse probability weighing was used for adjustment. An over-identification test for covariate balance verified that the propensity score model was correctly specified. Only covariates related to the outcomes (or both outcomes and treatment) were included in the model. Clinical data were stored in REDCap (Research Electronic Data Capture) at University of California-Los Angeles according to IRB and institutional guidelines. All analysis was performed using R software, version 3.0.2 (R Project for Statistical Computing) and SAS software, version 9.4 (SAS Institute Inc).

RESULTS

From June 2013 through April 2014, enough patients were accumulated to achieve 51 subjects in the control group and 47 subjects in the PEG intervention group. The study population characteristics are shown in Table 2. The PEG

Table 2. Study Population Characteristics

Variable	Polyethylene glycol group (n = 47)	Control group (n = 51)	p Value
Age, y, mean (SD)	50.1 (13.7)	51.3 (14.0)	0.66
BMI, n (%)			0.109*
Underweight (<18.5 kg/m^2)	3 (6)	0 (0)	
Healthy weight (18.5–24.9 kg/m^2)	12 (26)	22 (43)	
Overweight (25–29.9 kg/m^2)	22 (47)	21 (41)	
Obese (≥30 kg/m^2)	9 (19)	7 (14)	
Sex, male, n (%)	31 (66)	30 (59)	0.604
Race, n (%)			0.039
Caucasian	15 (32)	21 (41)	
African American	18 (38)	8 (16)	
Other	14 (30)	22 (43)	
Ethnicity, n (%)			<0.001*
Non-Hispanic	38 (81)	24 (47)	
Hispanic	9 (19)	25 (49)	
Unknown	0 (0)	2 (4)	
Cause of end-stage renal disease, n (%)			0.328*
Diabetes	6 (13)	8 (16)	
Hypertension	16 (34)	13 (25)	
Cystic disease	6 (13)	1 (2)	
Glomerulonephritis	5 (10)	10 (20)	
Urologic disease	1 (2)	3 (6)	
Other	9 (19)	12 (24)	
Unknown	4 (9)	4 (8)	
Diabetic, n (%)	13 (28)	24 (47)	0.077
Type of dialysis, n (%)			0.085*
Pre-emptive	4 (9)	3 (6)	
Hemodialysis	31 (66)	43 (84)	
Peritoneal dialysis	12 (26)	5 (10)	
Days on dialysis, mean (SD)†	1,884 (1,331)	2,040 (1,310)	0.579
Earlier abdominal surgery, n (%)	19 (40)	27 (53)	0.299
Length of surgery, min, mean (SD)	232 (34)	244 (39)	0.112
Donor type, n (%)			0.370*
Living	21 (45)	19 (37)	
Standard criteria donor	22 (47)	23 (45)	
Donor after cardiac death	4 (9)	4 (8)	
Expanded criteria donor	0 (0)	2 (4)	
Other (en bloc)	0 (0)	3 (6)	
Estimated blood loss, n (%)‡			0.396
<100 mL	11 (23)	16 (31)	
100–299 mL	32 (68)	28 (55)	
≥300 mL	4 (9)	7 (14)	
Intraoperative complication, n (%)	1 (2)	4 (8)	0.277*
Peritoneum entered, n (%)	2 (4)	2 (4)	1
Induction, n (%)			0.732
Basiliximab	32 (68)	32 (63)	
Thymoglobulin	15 (32)	19 (37)	
Intraoperative transfusion, n (%)	0 (0)	4 (8)	0.119*

*Fisher's exact test.
†Excluding pre-emptive patients.
‡One value missing replaced with mean of existing variables.

group had a significantly higher proportion of African-American and non-Hispanic subjects. There was also a nonsignificant trend toward diabetic and nonperitoneal dialysis subjects in the control group. Otherwise, the 2 cohorts were fairly well balanced with regard to preoperative characteristics.

Postoperative outcomes for the 2 study groups are shown in Table 1. The primary outcomes measure, time to bowel movement, for subjects receiving PEG was significantly shorter than that for the control group, by approximately 1 entire day (2.9 ± 1.1 vs 4.0 ± 1.3 days; $p < 0.001$). Figure 1 shows the Kaplan-Meier plot demonstrating this significant difference in the time to having a bowel movement between the 2 groups (log-rank $p < 0.001$). In the propensity score analysis, patients receiving PEG had bowel movements earlier (−1.06 ± 0.25 days; $p < 0.001$).

For our secondary outcomes measure, mean length of hospitalization was shorter in the PEG group by approximately 1 day (5.6 ± 2.9 vs 6.7 ± 4.4 days; $p = 0.042$). After adjustment via the propensity score analysis, there remained a clinically significant difference of more than 1 day in the hospital (−1.16 ± 0.27 days; $p < 0.001$).

Interestingly, the control group patients were more likely to start ambulating sooner (1.7 ± 1.1 vs 1.4 ± 1.3 days; $p = 0.011$). Important to note is that the time to starting a clear liquid diet was slightly sooner in the PEG group compared with the control, however, the time difference was small (18.0 ± 5.6 hours vs 23.3 ± 12.2 hours; $p = 0.007$).

The total opioid analgesic use (in morphine equivalents) during the transplantation admission is shown in Figure 2. Propensity analysis showed no relationship between PEG administration and narcotic use (−0.87 ± 1.1; $p = 0.43$). Mean patient-reported pain scores are shown in Figure 3. No relationship emerged between PEG administration and pain (−0.16 ± 0.21 days; $p = 0.44$). The addition of time to bowel movement and the other covariates (as mentioned) into the model and adjusting for clustering effects demonstrated that there was no significant difference between the 2 groups.

The graft function between the 2 groups was similar with regard to serum creatinine levels and rejection episode rates (Table 1). The PEG group trended toward having fewer postoperative complications, however, this was not significantly different between the 2 groups (21% vs 33%; $p = 0.268$). Also, the PEG group had a lower readmission rate within 30 days, which was almost significantly less than the control group (11% vs 27%; $p = 0.065$).

DISCUSSION

This study, to our knowledge, is the first to specifically address the use of PEG in kidney transplantation patients. We found that the use of PEG solution significantly reduced the time to return of bowel function in patients recovering from kidney transplantation when compared with a contemporary historic cohort. Our results showed a significant decrease in both time to a bowel movement and length of hospitalization. When potentially confounding patient variables were accounted for in propensity score models, PEG administration still decreased the time to bowel movements and length of hospitalization.

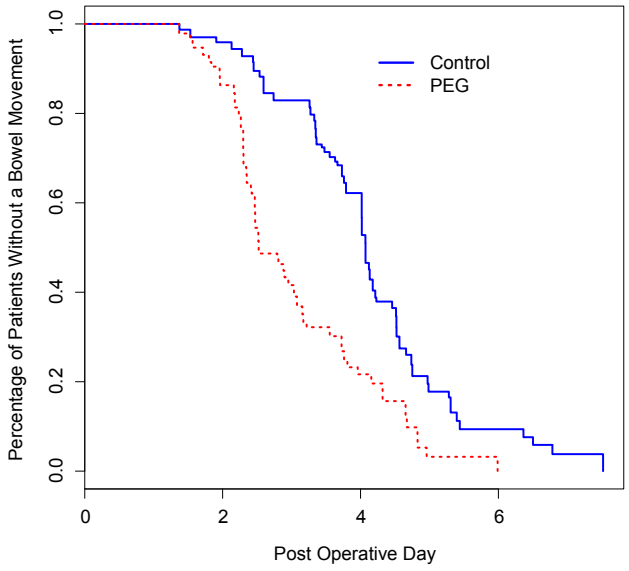

Figure 1. Kaplan-Meier plot of time to first bowel movement.

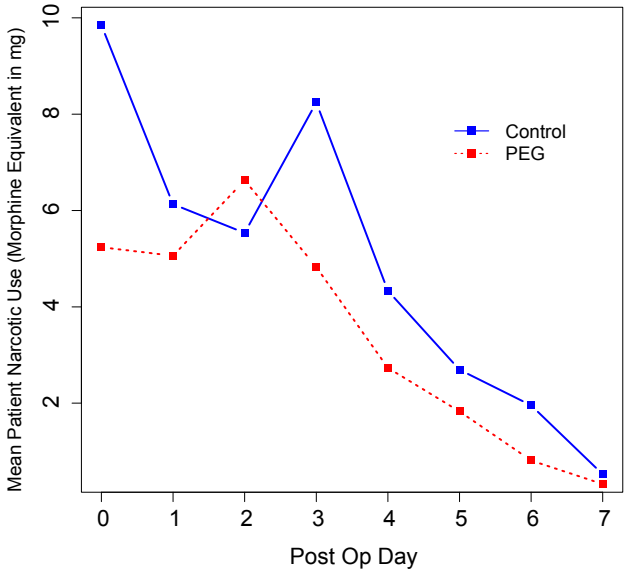

Figure 2. Use of narcotics during the postoperative period.

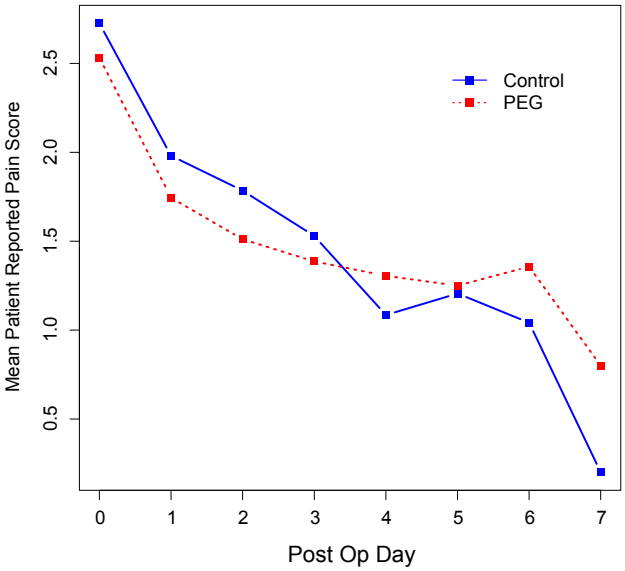

Figure 3. Patient-reported pain scores during the postoperative period.

No difference was found in patient-reported pain scores or narcotic use. Even though this study was not designed or powered to assess differences in readmission and postoperative complication rates, these occurred notably less frequently for patients given PEG when compared with the control group, suggesting that early bowel movements reduce additional perioperative complications and implying safety in use of PEG postoperatively in this patient population.

A number of factors specific to kidney transplantation and the kidney transplantation population inhibit return of bowel function. Kidney transplantation requires inhaled anesthetics along with paralytics for several hours, which contribute to postoperative bowel dysfunction.[10] Opioid analgesic use for pain control also contributes to slowing bowel movement through inhibition of the gastrointestinal μ-opioid receptors, particularly in the colon.[11] Even though the peritoneum is not routinely entered, irritation of the peritoneum is considered a major factor in bowel dysmotility after surgery.[12] Often, transplantation patients have advanced diabetes, which is associated with enteric nervous system dysfunction, which also contributes to poorer bowel motility.[13] In this study, PEG administration showed significant improvement in return to bowel function even when accounting for these factors (ie length of surgery, peritoneal involvement, use of peritoneal dialysis, diabetes, and opioid analgesic use).

The advantages of using PEG solution are the low cost, ease of administration, that it is well-tolerated, and has minimal side effects. The mean cost of daily PEG administration has been estimated to be approximately $1.00, and some of the newer, targeted pharmaceutical agents can cost in excess of $1,000.[14] In a clinical trial describing the pharmacokinetics of PEG, they showed minimal absorption of the drug overall, with no substantial differences in sex and age.[15] In our study, patients were noted to tolerate PEG well, particularly the pineapple flavor, although we did not measure if they were actually consuming the drug in an intention to treat model. We did not directly measure the impact of PEG on the dosing of immunosuppression agents directly in this study, however, clinical measures of graft function and rejection showed no overall difference between the 2 groups.

The interpretation of this study's results needs to be the context of the study design. The limitations in design (2-arm, single surgeon, nonrandomized) need to be considered as potential sources. However, the use of consecutive patients from a change in practice date, provided a quasi-randomization, and the 2 groups' characteristics were notably similar in this study. Of note, there was a trend toward more patients with diabetes in the control group. Intraoperative bleeding time and tranfusion requirements also trended toward being different between the 2 groups. However, we controlled for these variables in a multivariable model. Additionally, propensity score analysis was implemented to more aptly mimic a randomized design and eliminate selection bias. Care was taken in building models based on hypothesis testing to account for potential confounding factors.

Another potential limitation of the study surrounds the finding of decreased hospital stay by more than 1 day for patients who were given PEG. For renal transplantation patients, renal allograft function, immunosuppressant management, and social issues all have an effect on patient discharge. The individual needs and situations of each patient could have confounded the results. However, we attempt to adjust for this by controlling for complications (including delayed graft function) in the propensity score modelling.

Additional investigations should include analysis about the extent to which the PEG solution protocol was adhered to by the subjects, more specific information about narcotic pain medication administration (timing) in relation to patient-reported pain scores would also help refine our understanding of the impact of this treatment on patient recovery. Additionally, future studies should investigate the impact of PEG on transplant immunosuppression medications. Lastly, although a large, randomized, blinded, controlled study was beyond our initial investigative effort, we believe the findings in this study are strongly in favor of the treatment intervention and we have since adopted this practice as part of our routine postoperative care.

CONCLUSIONS

Administration of PEG postoperatively decreased time to first bowel movement and length of hospitalization. There is potential for decreased readmissions and postoperative complications with using this strategy for postoperative care, all of which lead to reduced patient morbidity and overall health care costs.

Author Contributions

Study conception and design: Treat, Baskin, Gritsch
Acquisition of data: Treat, Baskin
Analysis and interpretation of data: Treat, Baskin, Lin
Drafting of manuscript: Treat, Baskin
Critical revision: Treat, Baskin, Cohen, Del Rosario, Gritsch

Acknowledgment: The authors would like to thank the CITI REDCap administration for their help in designing and implementing the REDCap database used in this study. The authors would also like to thank the inpatient care teams for their hard work and efforts.

REFERENCES

1. Based on OPTN data as of March 12, 2015. Available at: http://optn.transplant.hrsa.gov/converge/latestData/rptData.asp. Accessed March 12, 2015.
2. Janjua HS, Hains DS, Mahan JD. Kidney transplantation in the United States: economic burden and recent trends analysis. Progr Transplant 2013;23:78–83.
3. Behrns KE, Kircher AP, Galanko JA, et al. Prospective randomized trial of early initiation and hospital discharge on a liquid diet following elective intestinal surgery. J Gastrointest Surg 2000;4:217–221.
4. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg 2008;13:569–575.
5. Noble EJ, Harris R, Hosie KB, et al. Gum chewing reduces postoperative ileus? A systematic review and meta-analysis. Int J Surg 2009;7:100–105.
6. Zingg U, Miskovic D, Pasternak I, et al. Effect of bisacodyl on postoperative bowel motility in elective colorectal surgery: a prospective, randomized trial. Int J Colorectal Dis 2008;23:1175–1183.
7. Sindell S, Causey MW, Bradley T, et al. Expediting return of bowel function after colorectal surgery. Am J Surg 2012;203:644–648.
8. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbrid LE, Molinoff PB, et al., eds. The Pharmacological Basis of Therapeutics. New York: McGraw-Hill; 2001:569–619.
9. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of C4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transpl 2014;14:272–283.
10. Condon RE, Cowles V, Ekbom GA, et al. Effects of halothane, enflurane, and nitrous oxide on colon motility. Surgery 1987;101:81–85.
11. Sternini C. Receptors and transmission in the brain-gut axis: potential for novel therapies. III. Mu-opioid receptors in the enteric nervous system. Am J Physiol Gastrointest Liver Physiol 2001;281:G8–G15.
12. Douglas DM, Mann FC. Effect of peritoneal irritation on the activity of the intestine. Br Med J 1941;1:227–231.
13. Camilleri M, Malagelada JR. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. Eur J Clin Invest 1984;14:420–427.
14. Drugs to treat constipation: which one is right for you? Consumer Rep 2013;22:1–2. Available at: http://www.consumerreports.org/cro/health/drugs/index.htm. Accessed October 15, 2015.
15. Pelham RW, Nix LC, Chavira RE, et al. Clinical trial: single- and multiple-dose pharmacokinetics of polyethylene glycol (PEG-3350) in healthy young and elderly subjects. Aliment Pharmacol Ther 2008;28:256–265.