Enhanced Recovery After Surgery Protocols Are Valuable in Pancreas Surgery Patients

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BACKGROUND: There is increasing interest in implementing comprehensive perioperative protocols, including preoperative optimization and education, perioperative goal-directed fluid management, and postoperative fast tracking, to enhance recovery after surgery. Data on the outcomes of these protocols in pancreatic surgery, however, are limited.

STUDY DESIGN: A retrospective review of a prospectively maintained pancreas surgery database at a single institution from August 2012 to April 2015 was undertaken. An enhanced recovery protocol was initiated in October 2014, and patients were divided into groups according to preprotocol or postprotocol implementation. Preoperative, intraoperative, and postoperative data were tabulated. Statistical analysis was performed with Student's *t*-test and Fisher's exact tests, as well as equality of variances where appropriate, using SAS System software (SAS Institute).

RESULTS: Three hundred and seventy-eight patients (181 men, mean age 54 years, BMI 28 kg/m^2) underwent elective pancreatic surgery during the study period, 297 patients preprotocol and 81 postprotocol. There were no significant differences in preoperative or intraoperative characteristics. Mean postoperative length of stay was significantly lower in the Enhanced Recovery After Surgery group (7.4 vs 9.2 days; $p < 0.0001$). Hospital costs were similarly lower in the Enhanced Recovery After Surgery group ($23,307.90 vs $27,387.80; $p < 0.0001$). Readmission (29% vs 32%) and pancreatic fistula (26% vs 28%) rates were similar between groups. Delayed gastric emptying was lower in the Enhanced Recovery After Surgery group (26% vs 13%; $p = 0.03$).

CONCLUSIONS: Implementation of an enhanced recovery after pancreatic surgery protocol significantly decreased length of stay and hospital cost without increasing readmission or morbidity. Despite patient complexity and the potential need for individualization of care, enhanced recovery protocols can be valuable and effective in high-risk patient populations, including pancreatic surgery patients. (J Am Coll Surg 2016;222:658–664. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Enhanced Recovery After Surgery (ERAS) protocols are comprehensive multimodal perioperative care pathways designed to optimize patient outcomes after major surgery. Enhanced Recovery After Surgery protocols are multidisciplinary in design, necessarily involving surgeons and anesthesiologists, along with the essential role of midlevel providers, dietitians, and nursing staff. Importantly, they are meant to represent best-practice perioperative care by incorporating evidence-based elements and by standardization of care.

The ERAS protocols are differentiated from "fast-track" protocols in that the latter are surgeon-driven, postoperative pathways that are intended to achieve early discharge.[1] In contrast, ERAS protocols are multidisciplinary, include preoperative, intraoperative, and postoperative elements, and are designed to optimize outcomes by reducing surgical stress and supporting organ function. Although there are many components to an ERAS pathway, 2 essential and relatively novel components are the restriction of IV fluid administration (both in the intraoperative and postoperative period) and preoperative

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carbohydrate loading to avoid insulin resistance. Successful incorporation of these 2 elements has been shown to independently predict improved outcomes.[2]

The ERAS concept evolved in the 1990s in Europe, with particular focus on colorectal surgery. A recent meta-analysis of 16 randomized controlled trials of ERAS protocols in colorectal surgery, including 2,376 patients, reported a significantly decreased risk of complications (relative risk = 0.60), particularly pulmonary and cardiovascular (relative risk = 0.40) and decreased hospital stay (−2.28 days), without increasing readmissions or mortality.[3] The relevance and outcomes of ERAS protocols after pancreas surgery, however, have not been as well demonstrated. Concerns have been reasonably raised for potentially increased morbidity (eg, by aspiration with early feeding protocols), increased readmission rates (with early discharge), and increased mortality (via failure to rescue with early discharge). This study is therefore designed to evaluate outcomes after implementation of an ERAS protocol for elective pancreas surgery, with particular attention to safety (morbidity, mortality) and efficiency (length of stay, cost).

METHODS

A retrospective review of a prospectively maintained pancreas surgery database, including patients undergoing pancreas surgery at a single institution from August 2012 to April 2015, was undertaken. An ERAS protocol was initiated in October 2014. For the study analysis, patients were divided into groups according to whether they underwent surgery preprotocol (pre-ERAS) or postprotocol (ERAS) implementation. Preoperative, intraoperative, and postoperative data were tabulated and compared between the groups. Cost and length of stay data for the study patients were obtained from the hospital administrative database. Statistical analysis was performed with Student's *t*-test and Fisher's exact tests, as well as equality of variances, where appropriate, using SAS System software (SAS Institute). This study was performed under the approval of the IRB for the evaluation of human subjects.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Medical University of South Carolina. REDCap (Research Electronic Data Capture) is available via the South Carolina Center for Translational Research, which receives Biomedical Informatics Services grant support from the NIH (NIH/NCATS UL1TR000062) ERAS protocol (Table 1)

Preoperative elements

In the preoperative clinic visit, patients undergo formal, standardized education on the disease and operative procedure by the ERAS nurse, including specific expectations for the perioperative course, to facilitate patient responsibility and participation in the process. Patients are seen by a dietitian for an individualized needs assessment. Patients are prescribed a 5-day course of immunomodulating nutritional supplements, which are not only enriched in protein, but also omega-3 fatty acids, specific amino acids (glutamine and arginine), and nucleotides. Preoperative carbohydrate loading is also prescribed, with a clear liquid carbohydrate-rich supplement on the evening before surgery, as well as 3 hours before surgery. Regional anesthetics (epidural catheters for open procedures, transversus abdominus plane blocks for laparoscopic) are maximally used to minimize narcotic use. Patients are given warm blankets to promote normothermia.

Intraoperative elements

Normothermia measures are continued from the preoperative room, including active warming blankets, ambient room temperature, and warm IV fluids. Chemical and mechanical venous thromboembolism prophylaxis is administered. Standard surgical antibiotic prophylaxis is respected. A wound protector is used on laparotomy incisions and laparoscopic extraction sites. Intraoperatively, patients are given pre-emptive antiemetics and adjunctive non-narcotic analgesics. Perioperative goal-directed IV fluid management is undertaken using hemodynamic monitoring via the arterial line or with noninvasive plethysmography. Maintenance IV fluid is administered at a restricted rate and the stroke volume variations are considered in any adjunctive fluid administration (Fig. 1).

Postoperative elements

Nasogastric tubes are avoided (laparoscopic distal pancreatectomy) or removed early, and Foley catheters are similarly removed early (postoperative day 1). Prolonged postoperative fasting is avoided, with full liquids beginning postoperative day 1 and patient-choice diet postoperative day 2. Intravenous fluid restriction is continued in the postoperative period with specified rates and parameters for fluid bolus administration, and permissive relative oliguria. Early ambulation is required.

RESULTS

Baseline characteristics and study groups

During the study time period (August 2012 through April 2015), 378 patients underwent elective pancreatic resection (197 women, mean age 54 years, mean BMI 27.7 kg/m^2). Two hundred and ninety-seven patients underwent surgery before initiation of the ERAS protocol (pre-ERAS group, August 2012 through September 2014) and 81 patients underwent surgery after initiation

Table 1. Enhanced Recovery after Pancreas Surgery Protocol

Phase and protocol element	Notes
Preoperative	
Patient education	Explanation of disease Summary of operative conduct and risks Detailed description of expectations for progress in the postoperative course
Individual nutritional assessment	Dietitian performed evaluation of nutritional status, counseling for preoperative optimization
Immunomodulating nutritional supplementation	Supplement 3 times per day for 5 days preoperatively
Carbohydrate loading	Clear liquid carbohydrate-rich drink taken orally the night before surgery and again 3 hours before surgery
Regional anesthetic	Epidural catheter for open surgery, transversus abdominus plane block for laparoscopic procedures
Normothermia protocol	Warm blankets
Venous thromboembolism prophylaxis	Heparin 5,000 U subcutaneously Sequential compression devices on bilateral lower extremities
Intraoperative	
Normothermia protocol	Elevated ambient room temperature, warmed IV fluids, forced air warmer
Antibiotic prophylaxis	Cefazolin and metronidazole (piperacillin-tazobactam for patients with earlier endoscopic biliary or pancreatic manipulation) before incision, within 1 hour
Wound protector	To maintain moisture of subcutaneous tissues and protect them from exposure
Pre-emptive antiemetics	Ondansetron, dexamethasone
Adjunctive non-narcotic analgesics	Ketorolac, IV acetaminophen, gabapentin, cyclo-oxygenase 2 inhibitor
Goal-directed fluid administration	Using stroke volume variation to determine IV fluid administration (see Fig. 1)
Postoperative	
Avoidance or early removal of nasogastric tube	No nasogastric tube for laparoscopic distal pancreatectomy, for other pancreas procedures, nasogastric tube removed on postoperative day 1
Avoidance or early removal of surgical drains	Drain amylase evaluated postoperative day 3 Drain removed if amylase content <3 times normal
Early removal of Foley catheter	Foley catheter removed morning of postoperative day 1
IV fluid restriction	Postoperative day 0: normal saline 100 mL/h Postoperative day 1 and 2: dextrose 5% in 0.45% normal saline (D51/2NS) 75 mL/h Postoperative day 3: Heplock
Early diet advancement	Full liquids postoperative day 1 Patient choice diet postoperative day 2
Early ambulation	Sitting up on edge of bed postoperative day 0 Out of bed walking postoperative day 1

of the protocol (ERAS group, October 2014 through April 2015). Demographic characteristics and preoperative diagnoses were not different between the groups (Tables 2 and 3).

Intraoperative data

Intraoperative patient characteristics as well as operative conduct were similar between the pre-ERAS and ERAS groups (Table 4).

Postoperative data

After surgery, patients in the pre-ERAS and ERAS groups had similar overall morbidity rates, including wound infection, pneumonia, and pancreatic fistula rates. There was a significantly lower rate of delayed gastric emptying in the ERAS group than in the pre-ERAS group (13% vs 26%; $p = 0.025$). Mean length of stay was also decreased in the ERAS group (7.4 vs 9.2 days; $p < 0.0001$). The readmission rate and 90-day mortality rate were

- Open cases: Balanced crystalloid (Plasmalyte or LR) at 5cc/kg/hr (maximum 500cc/hr)
- Laparoscopic cases: Balanced crystalloid at 3cc/kg/hr (maximum 250cc/hr)
- Hemodynamic monitoring through case, with determination of stroke volume variation (SVV). Arterial line device or finger cuff utilized where appropriate
- If patient becomes hypotensive (mean arterial pressure 20% below baseline) and SVV > 12, 250 cc bolus of balanced crystalloid given over 15 minutes. Repeat bolus if no improvement. If continued hypotension after 2 boluses and cardiac index < 2.5, add vasopressor
- Reduce balanced crystalloid to 2cc/kg/hr during closing

Figure 1. Intraoperative goal-directed fluid management.

unchanged from before protocol implementation (Table 5). Notably, hospital costs were significantly lower in the ERAS group than in the pre-ERAS group ($23,307.90 vs $27,387.80; $p < 0.0001$).

Neoplasia vs chronic pancreatitis

A subgroup analysis was undertaken evaluating patients with neoplasia as the primary indication for pancreas surgery and those with chronic pancreatitis. There were 121 patients in the pre-ERAS group who underwent pancreas surgery for a neoplastic process (66 women, mean age 63 years) and 38 patients in the ERAS group who underwent surgery for neoplasia (21 women, mean age 62 years). Preoperative and intraoperative characteristics were similar between the 2 groups (Table 6). In the postoperative period, complication rates were not different, including postoperative pancreatic fistula, delayed gastric emptying, pneumonia, and soft tissue infection rates. Length of stay was significantly decreased in the ERAS group (mean 6.6 vs 8.7 days; $p = 0.04$). Readmission rates were not different between the groups (Table 7).

There were 176 patients in the pre-ERAS group who underwent pancreas surgery with chronic pancreatitis as the primary indication (93 women, mean age 47 years) and 43 patients in the ERAS group (16 women, mean age 47 years). Preoperative and intraoperative characteristics were similar between the 2 groups (Table 8). In the postoperative period, complication rates were similar except for delayed gastric emptying, which was lower in the ERAS group (11% vs 27%; $p = 0.03$). Length of stay and readmission rates were not different between groups (Table 9).

Table 2. Demographic Characteristics of Preprotocol and Postprotocol Groups

Characteristic	Pre-ERAS group	ERAS group	p Value
n	297	81	
Male, n (%)	138 (46)	44 (54)	0.2
Mean age, y	54	54	NS
Mean BMI, kg/m^2	27.5	28.4	NS
Tobacco use, n (%)	126 (42)	42 (52)	0.13
Mean albumin, g/dL	3.6	3.6	NS

ERAS, Enhanced Recovery After Surgery.

DISCUSSION

The elemental surgical principle that it is the system, and not solely the surgeon, that drives successful surgical outcomes is not a new concept. Jolly[4] described this principle in his 1941 treatise on field surgery in the Spanish Civil War. "It is worth emphasizing," Jolly wrote, "that the recovery rate in abdominal cases depends less on the individual ability of the surgeon than on any other single factor…. The all-important factor is the system, not the surgeon." What Jolly observed in abdominal cases on the battlefield is even more true in pancreatic cases observed in the modern tertiary care medical center. Enhanced Recovery After Surgery is the system that drives excellence for the individual surgeon. The ERAS system works. Prospective studies have shown that well-implemented ERAS protocols decrease length of stay and costs without affecting readmission rates or compromising patient safety in colorectal and other types of abdominal surgery.[5-8] Enhanced Recovery After Surgery protocols have an equally important role in complex surgery, such as pancreas resection and drainage procedures.

Table 3. Preoperative Diagnosis of Preprotocol and Postprotocol Groups

Characteristic	Pre-ERAS group, n	ERAS group, n	p Value
Pancreatic adenocarcinoma	37	14	NS
Cholangiocarcinoma	8	3	NS
Duodenal adenocarcinoma	5	1	NS
Ampullary adenocarcinoma	2	1	NS
Intraductal papillary mucinous neoplasm	30	6	NS
Pancreatic neuroendocrine tumor	16	7	NS
Mucinous cystic neoplasm	5	1	NS
Serous cystadenoma	6	2	NS
Pancreatitis	176	42	NS
Other	12	4	NS

ERAS, Enhanced Recovery After Surgery.

Table 4. Intraoperative Data for Preprotocol and Postprotocol Groups

Characteristic	Pre-ERAS group	ERAS group	p Value
Mean estimated blood loss, mL	431	511	NS
Mean length of surgery, min	190	191	NS
Surgery performed, n			
Pancreatoduodenectomy	82	27	NS
Distal pancreatectomy	93	29	NS
Total pancreatectomy	48	11	NS
Lateral pancreaticojejunostomy	24	5	NS
Necrosectomy	21	3	NS
Transduodenal sphincteroplasty	22	2	NS
Other	7	4	NS

ERAS, Enhanced Recovery After Surgery.

Enhanced Recovery After Surgery protocols have many attributes that contribute to the cost and quality of surgical care. Overall hospital length of stay is decreased due to several factors. Preoperative patient education facilitates proper patient expectations and empowers the patient to be an active participant in their care. Preoperative immunomodulation blunts the inflammatory response to surgical trauma[9,10] and carbohydrate loading ameliorates the catabolic surgical state, avoiding perioperative insulin resistance.[11] Regional anesthetics and non-narcotic adjunctive analgesics limit the narcotic contribution to delays in return of bowel function.[12] Perioperative fluid restriction limits visceral edema and can facilitate early gastrointestinal function.[13,14] Enteric tube avoidance and early gastric tube removal speeds time to oral intake.[15,16] Early ambulation is a key factor in limiting deconditioning and assisting with return of bowel function. Hospital cost is closely linked with hospital stay and decreases in cost are primarily attributable to the decreased hospital length of stay.

Table 5. Postoperative Data for Preprotocol and Postprotocol Groups

Characteristic	Pre-ERAS group	ERAS group	p Value
Length of stay, d, mean	9.2	7.4	0.0001
ICU length of stay, d, mean	1.85	1.16	NS
Delayed gastric emptying, %	26	13	0.025
Wound infection, %	6	9	NS
Pneumonia, %	7	8	NS
Pancreatic fistula, %	26	28	NS
Pancreatic fistula, grade C, %	3	1	NS
Overall complication rate, %	63	59	NS
Significant complication rate, %	25	21	NS
Readmission, %	29	32	NS
Mortality, n	2	0	NS

ERAS, Enhanced Recovery After Surgery.

Table 6. Preoperative and Intraoperative Characteristics of Patients Undergoing Pancreas Surgery for Neoplasia

Characteristic	Pre-ERAS group	ERAS group	p Value
n	121	38	
Male, n (%)	55 (45)	17 (45)	NS
Age, y, mean	63	62	NS
BMI, kg/m^2, mean	29.3	28.6	NS
Tobacco use, %	40	47	NS
Albumin, g/dL	3.6	3.6	NS
Estimated blood loss, mL	446	615	NS
Operative time, min	222	202	NS

ERAS, Enhanced Recovery After Surgery.

Not surprisingly, the difference in length of stay was found on subgroup analysis to be more significant in the patients undergoing surgery for tumor than for those undergoing surgery for chronic pancreatitis. Length of stay in surgery for chronic pancreatitis is related to a long disease course before surgery, including preoperative pain and longstanding gut dysfunction, which is less likely to be affected by ERAS protocol measures. Patients undergoing surgery for neoplastic disease, however, are more likely to achieve measurable benefit from the protocol measures reducing stress and limiting perioperative organ dysfunction.

Delayed gastric emptying rates were found to be lower with the ERAS protocol for many reasons. Early nasogastric tube removal and early diet advancement play a key role. Perioperative fluid restriction, preoperative carbohydrate loading, avoidance of narcotic analgesics, and early ambulation also contribute to improved gastric emptying after operation and help to expedite patient discharge.

Interestingly, the difference in delayed gastric emptying was found on subgroup analysis to be more significant in patients undergoing surgery for chronic pancreatitis than in those with tumors. The reasons for this finding are

Table 7. Postoperative Outcomes of Patients Undergoing Surgery for Neoplasia

Outcome	Pre-ERAS group	ERAS group	p Value
Overall complications, %	65	65	NS
Significant complications, %	22	21	NS
Pancreatic fistula, %	27	30	NS
Delayed gastric emptying, %	22	16	NS
Soft tissue infection, %	6	8	NS
Pneumonia, %	6	0	NS
Length of stay, d, mean	8.7	6.6	0.03
Readmission, %	25	26	NS

ERAS, Enhanced Recovery After Surgery.

Table 8. Preoperative and Intraoperative Characteristics of Patients Undergoing Surgery for Chronic Pancreatitis

Characteristic	Pre-ERAS group	ERAS group	p Value
n	176	43	
Men, n (%)	83 (47)	16 (37)	0.09
Age, y	47	47	NS
BMI, kg/m^2	26	28	NS
Tobacco use, n (%)	76 (43)	23 (53)	NS
Albumin, g/dL	3.5	3.6	NS
Estimated blood loss, mL	421	418	NS
Operative time, min	168	181	NS

ERAS, Enhanced Recovery After Surgery.

unclear. Chronic pancreatitis patients did have lower postoperative pancreatic fistula rates, which is a primary risk factor for delayed gastric emptying.

It is notable that these improvements in outcomes were demonstrated with protocol implementation, as many of the elements of the protocol were applied, although inconsistently, before ERAS protocol implementation. Preoperative immunomodulating nutritional supplementation and regional anesthetics were used at our institution in the pre-ERAS era. Intraoperative normothermia protocols and antibiotic and venous thromboembolism prophylaxis guidelines were already in place. Postoperative "fast-track" order sets were also standardized. The salient difference with the ERAS protocol was the refinement and consistent use of these pre-existing elements, along with the implementation of novel elements, including preoperative carbohydrate loading, use of adjunctive non-narcotic analgesics, and perioperative fluid restriction. This was achieved with standard education and collaboration between patients, surgeons, residents, nurses, anesthesiologists, intensivists, pharmacists, nutritionists, physical therapists, case managers, and discharge planners in the preoperative, operative, and postoperative periods.

Success of ERAS is due to a team approach, standardization of care, and honing of evidence-based practices.

Table 9. Postoperative Outcomes of Patients Undergoing Surgery for Chronic Pancreatitis

Outcome	Pre-ERAS group	ERAS group	p Value
Overall complications, %	63	65	NS
Severe complications, %	29	23	
Postoperative pancreatic fistula, %	17	20	NS
Delayed gastric emptying, %	28	11	0.03
Soft tissue infection, %	5	12	
Pneumonia, %	7	16	
Length of stay, d	10.7	9.05	
Readmission, %	30	29	

ERAS, Enhanced Recovery After Surgery.

Enhanced Recovery After Surgery protocols necessarily entail multidisciplinary collaboration. The team approach to pancreatic disease has been well-realized in the preoperative setting, as exemplified by role of the multidisciplinary tumor board in providing optimal care for pancreatic cancer patient.[17] Improved communication and collective intelligence can contribute to more thoughtful and effective perioperative patient care protocols. Team building to allow for standardization of the important elements of the anesthesia team plan for pain and fluid management is basic to a strong ERAS foundation.

Enhanced Recovery After Surgery protocol development represents an ideal opportunity to review current surgical practice and avoid anecdotal medicine. Surgery and surgical patient care are steeped in tradition. Pancreatic surgery in particular resides in the temple of surgical heroes and experience-based medicine. It might be carping to comment that the art of surgery is long and experience fallacious; it is cogent to highlight that the modern surgeon knows the value of evidence-based practice. By systematically evaluating the available data at each step of perioperative care, one can move toward best practice; where evidence is lacking, opportunity for further study is identified. In the long run, with careful study of the individual protocol elements and protocol refinement, optimal perioperative care will be achieved to facilitate improved outcomes beyond decreased length of stay, cost, and delayed gastric emptying.

Standard process is critical to the success of the ERAS pathway, even more than the specific elements of the protocol itself. Protocols limit human errors of omission and commission, particularly in the complex and labor-intensive perioperative course of the pancreas surgery patient.

This study is limited by the relatively short time frame assessed and the heterogeneity of pancreatic cases included. Subgroup analyses are limited due to the cohort size.

CONCLUSIONS

Enhanced Recovery After Surgery protocols are effective in pancreatic surgery. They improve efficiency, hospital length of stay, and costs. Enhanced Recovery After Surgery is safe. Enhanced Recovery After Surgery decreases postoperative morbidity, especially delayed gastric emptying. Careful study will increase understanding, which will lead to additional protocol improvements to achieve optimal perioperative patient care for the patient with pancreatic disease. Enhanced Recovery After Surgery protocols are a new implementation of the old surgical principle: "In abdominal cases, the all-important factor is the system, not the surgeon."

Author Contributions

Study conception and design: Morgan, Lancaster, Clark, McSwain, Adams

Acquisition of data: Morgan, Lancaster, Walters, Owczarski

Analysis and interpretation of data: Morgan, Lancaster, Adams

Drafting of manuscript: Morgan, Lancaster, Adams

Critical revision: Walters, Owczarski, Clark, McSwain

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Discussion

DR TIMOTHY M PAWLIK (Baltimore, MD): Our group at Johns Hopkins recently introduced an enhanced recovery after surgery (ERAS) pathway for open hepatic surgery that includes the same elements as the pathway proposed here such as preoperative carbohydrate loading, minimization of IV fluids, and increased use of regional anesthesia. Similar to your presented data, we showed that among patients undergoing an open hepatectomy, the introduction of ERAS was associated with a reduction in opioid use, shorter hospital stay, and decreased hospital costs.

Can you give us some idea about how the ERAS pathway was implemented? Were parts of the pathway "hard wired" into the electronic order enter system? What type of nursing or physician assistant support did you have? Having implemented an ERAS pathway ourselves at Hopkins, it was our experience that additional institutional resources are necessary to implement a successful ERAS pathway. I would be curious about your experience at the Medical University of South Carolina (MUSC). How much hospital support was provided, and what resources did you have?

The ERAS pathway has many moving parts and pieces. Do you have any data on overall compliance with the pathway? In other words, how often was the ERAS pathway followed completely? Were there parts of the pathway that had higher vs lower compliance? Did the ERAS pathway differ for patients undergoing Whipple vs distal pancreatectomy?

Following on this question, what element of the ERAS pathway do you and the group at MUSC think is the most important? Specifically, what parts of the pathway do you think are most likely responsible for the decreased incidence of gastric emptying and shorter length of stay? Is it the preoperative carbohydrate loading, or avoidance of opioids?

In our study on ERAS we noted cost savings in a number of different areas including medical supply costs. Do you have any more granular data on where the ERAS protocol's associated cost savings are coming from at your institution?

Finally, you performed some subset analyses according to indication for pancreatic resection and looked at outcomes separately among only patients with malignant vs benign disease. However, in these subset analyses, your patient numbers are small, with fewer than 50 patients in each of these groups. Do you think it is too early