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What is the Best Pain Control After Major Hepato-Pancreato-Biliary (HPB) Surgery?

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Keywords

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INTRODUCTION

In the modern era, hepato-pancreato-biliary (HPB) surgery has become safe with significant reductions in morbidity and mortality at high volume centers for both liver and pancreas surgery. While laparoscopic surgery has provided a safe approach with superior pain control laparotomy is still needed for the majority of HPB operations. Inadequate pain control is not only associated with poor patient experience but contributes to inferior outcomes. Specifically, inadequate pain control affects the neuroendocrine stress response, increases complication rates, and prolongs length of stay. Furthermore, there is an ongoing opioid epidemic and all fields of medicine should strive to reduce narcotic use to limit transformation into chronic opiate dependence. As such, successful pain control after HPB surgery continues to be a challenge and rigorous studies evaluating postoperative results are needed.

The following article reviews the modalities debated to be the best strategies for pain control after major HPB surgery, as well as a discussion of other important considerations when executing these plans.

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Biologic Effects of Opiates

There are multiple reports in the literature on the negative effects opioids can have on patient function and on cancer biology.[1,2] Emerging data points to direct opioid-cellular interactions that explain these observations. Opiates have been reported to activate vascular endothelial growth factors (VEGF), directly stimulating cancer growth and metastatic potential.[1–3] Moreover, worse survivals in patients with breast and lung cancer were reported when the tumors expressed certain polymorphism of the μ-opioid receptor (MOR).[4,5] Additional studies focused on the effects of MOR on epithelial mesenchymal transition (EMT),[1] which is a necessary oncogenic process involving loss of cell-cell adhesion, subsequent loss of baso-apical polarization, cytoskeletal remodeling, and increased cell motility and transcription factors for cancer cell growth and metastasis.[6] MOR regulates opioid and epidermal growth factor (EGF) signaling, which is important for human cancer cell proliferation and migration. In addition, human cancer cells treated with opioids exhibited an increase (snail, slug, vimentin) and decrease in other (ZO-1 and claudin-1) protein levels consistent with an EMT phenotype.[1] Taken together, these results suggest that opioid-MOR interactions may have a direct effect on the proliferation, migration and EMT transition for cancer progression. These findings have led to human clinical studies investigating the effects of analgesia agents on cancer outcomes including recurrence and overall survival.

Opioid Epidemic

Currently, the United States of America is suffering from a national crisis with opioid abuse with more than 600,000 deaths to date, and with a prediction of 180,000 additional mortalities by 2020.[7] The opioid epidemic is accounting for an annual cost of over $50 billion per year of treating prescription opioid use and abuse.[8] Moreover, opioid naïve surgical patients are at high risk for becoming chronic opioid users,[9] and minimizing the need for narcotics in the hospital and after discharge could aid in combatting this major issue.

Intravenous Patient Controlled Analgesia (IV PCA)

Intravenous patient controlled analgesia (IV PCA) is one of the most common and “conventional” strategies for pain control post-operatively. Unfortunately, IV PCA alone can only provide short periods of pain relief; thus, it may not be the optimal method for extended pain control in the immediate post-operative recovery period. With this strategy alone, patients may consume larger amounts of opiates, increasing risk for nausea, vomiting, ileus, chronic opiate needs after discharge, delay in return of bowel function, and delay in post-operative mobilization. Now, many adjuncts (ie. continuous infiltrating wound catheters, nonsteroidal anti-inflammatory drugs, transversus abdominis plane infiltration) are used in conjunction with this modality or it is increasingly replaced by other strategies such as epidural analgesia (EA) to alleviate this concern.

Continuous Infusion through a Wound Catheter (CIWC)

One retrospective study of 498 patients undergoing liver surgery comparing continuous infusion of bupivacaine through a wound catheter (CIWC)+ IV PCA vs. Epidural Analgesia (EA), showed similar pain control, but lower amounts of opiate consumption in the CIWC + IV PCA group. However, this retrospective study was significantly weighted towards the CIWC + IV PCA group (n=429) and was at high risk for selection bias.[10] Currently, a trial in the Netherlands is underway testing noninferiority of CIWC + IV PCA to EA after elective HPB surgery via laparotomy in an Enhanced Recovery (ER) setting.[11] The primary endpoint of this study is Overall Benefit of Analgesic Score, a composite endpoint of pain intensity, opioid related adverse effects, and patient satisfaction during postoperative days 1 to 5. Secondary endpoints include length of stay, number of patients with severe pain, and the need for rescue medication.

Epidural Analgesia (EA)

EA provides pain control through blockage of both visceral and somatic pain.[12] Historically, it was criticized by some due to low-level evidence from retrospective studies reporting increased risk of epidural related complications including hypotension, ICU readmissions, and a need for excessive fluid and blood product administration.[13–15] Sugimoto et al. reported epidural dysfunction to be associated with an increase in overall complications ($p<0.001$), pancreas-related complications ($p=0.041$), and non-pancreas-related complications ($p=0.001$). However, this study was retrospective, from a small cohort of patients (n=72), and reported an abnormally high rate of epidural dysfunction (49%). A larger retrospective study of 367 patients undergoing partial hepatectomy were examined and identified the EA group (vs. no EA) had a lower mean arterial pressure in recovery (86.6 mmHg vs. 94.5 mmHg, $p<0.001$) and higher percentage of patients receive packed red cells during the hospital course (44.5% vs. 27.9%, $p<0.001$), respectively. Subsequent multivariate analysis identified EA among many other variables (age > 65 years, American Society of Anesthesiologists grade >2, starting hematocrit <38%, operative time > 300 minutes, blood loos > 1 liter) to be at increased odds for requiring blood transfusion. Of note, these data come outside of the modern era of striving for zero transfusions during hepatectomy,[16] and reports an overall transfusion rate of 39%. Furthermore, the study's EA protocol utilized a high concentration of 0.1% bupivacaine, which is now typically started at significantly lower concentrations.

One large retrospective cohort study reviewed 8,610 PD's in 2009 from a Nationwide Inpatient Sample from the Agency for Healthcare Research and Quality identified the use of EA was associated with a lower odds (OR 0.61 CI 0.37–0.99, $p=0.044$) of complication including death.[17] This same analysis revealed that patients who received EA (vs. no EA) also had a shorter length of stay (13.0 days vs. 15.7 days, $p<0.001$) and lower costs ($120,656 vs. $152,905, $p<0.001$), respectively. Subsequently, a more recent analysis from the same national database included all HPB operations performed in 53,712 patients between 2000 and 2012.[18] Results showed that patients who received EA were less likely to have sepsis (OR 0.75 CI 0.61–0.94), postoperative hemorrhage (OR 0.79 CI 0.66–0.94), postoperative pneumonia (OR 0.73 CI 0.60–0.90), respiratory failure (OR 0.89 CI 0.79–

0.99) and liver failure (OR 0.69 CI 0.49–0.98), all p<0.05. No difference was observed with in-hospital mortality among patients who underwent hepatectomy, but a significant difference was observed in patients who received an EA vs. no EA for pancreatic operations (2.1% vs. 3.1%, p<0.001 respectively). This study revealed a greater LOS in patients who received an EA (8 days) vs. those without EA (7 days), p<0.001.

More recent evidence has demonstrated EA to provide superior pain control based on two randomized controlled trials after HPB surgery.[19,20] The University of Edinburgh conducted a randomized clinical trial of CIWC +IV PCA vs. EA following liver resection surgery that showed superior pain control in the epidural arm and lower overall use of narcotics, while overall complication rates were similar.[20] In contrast, in this small randomized study of 55 patients, the patients in the CIWC + IV PCA arm fulfilled discharge criteria faster than patients who received epidural (4.5 days vs. 6.0 days. p=0.044). Of note, this study did not include assessment of patient satisfaction and recovery through a validated patient-reported outcome tool.

At the University of Texas MD Anderson Cancer Center, a randomized clinical trial was conducted comparing EA vs. IV PCA in a cohort of patients who underwent major HPB surgery (largely hepatic resection).[19] Ultimately, this study of 140 patients reported EA (vs. IV PCA) to be associated with superior area under the curve pain control scores (Figure 1A: 78.6 pain-hours vs. 105.2 pain-hours), less severe pain event rates, improved patient-reported outcomes, reduced total narcotic usage measured in oral morphine equivalents (Figure 1B: 155.3 mg vs. 429.8 mg), while having similar analgesia-related events, surgical complications, and length of stay. Of note, only one patient in the EA arm experienced transient renal insufficiency among the thirteen patients who experienced analgesia-related events. Importantly, this trial used a lower concentration of bupivacaine (0.075%) to protect against clinically significant hypotension episodes while still maintaining adequate pain control, a balance that should be considered with all epidural protocols.

The use of epidural analgesia has potential benefits beyond better pain control, patient reported outcomes, and decreased narcotic use. In a study by Zimitti et al., the effect of epidural analgesia on recurrence free survival and overall survival was analyzed.[21] In this study, 510 patients who had colorectal liver metastasis received either epidural analgesia or intravenous patient controlled analgesia (Figure 2). On multivariate analysis, the use of epidural analgesia was an independent predictor of a longer RFS (HR 0.76 CI:0.58–0.98; p=0.036, however, the use of epidural analgesia did not have a significant effect on overall survival (HR 0.72 CI:0.49–1.07; p=0.102). In this study, length of hospital stay or postoperative complications was not affected by the use of epidural analgesia.

Intrathecal Analgesia

Intrathecal analgesia has long been a mainstay in providing analgesia for open abdominal surgery, though not extensively studied in HPB surgery. The risks involved with injection of intrathecal opioids or local anesthetics carry the similar risks as that of epidural injection. One recent randomized controlled trial of 49 patients undergoing open HPB surgery compared intraoperative intrathecal morphine vs. intravenous opioids during surgery (IV

remifentanil infusion during surgery followed by IV bolus of morphine, 0.15 mg/kg before the end of surgery). The study showed pain scores to be significantly worse in patients who received intravenous opioids at various time points till postoperative day 3.[22] Although not examined in HPB surgery, one randomized study failed to demonstrate non-inferiority of intrathecal morphine + IV PCA to EA with respect to pain control, ambulation, postoperative ileus, and pulmonary complications among patients undergoing gastrectomy.[23]

TAP Infiltration

Transversus Abdominis Plane (TAP) infiltration is an emerging novel technique to provide analgesia to the anterior abdominal wall through coverage of somatic pain. The block is performed with the ultrasound guided injection of local anesthetic into the fascial plane (TAP) separating the transverse abdominis and the internal oblique muscles (Figure 3). Furthermore, the TAP block is associated with lesser degree of perioperative hypotension when compared to epidural analgesia, and does not cause urinary retention. The procedure is easy to perform, safe, and can be utilized in patients who are anticoagulated (unlike epidurals). Previously, a prolonged effect was impossible with this single shot infiltration technique using conventional local anesthetic, but with the development of liposomal bupivacaine, an extended effect can now be provided.[24]

Currently, there are few studies, all low-level evidence with limited power and retrospective in design, comparing TAP to EA.[25–27] Two of these studies showed comparable analgesia pain control between the two modalities, but all reported a larger use of total supplemental opioids in the TAP group.[26,27] Most recently, a study by Ayad et al conducted a noninferiority study comparing EA vs. TAP vs. IV PCA in patients undergoing major lower abdominal surgery. Among the 318 patients who were selected for analysis, TAP infiltration was noninferior to EA on both primary outcomes of pain scores and opioid consumption ($p<0.001$).[25] Additionally, TAP infiltration was noninferior to IV PCA on pain scores but was not superior on opioid consumption ($p=0.37$). Lastly, the study did not find noninferiority of EA over IV PCA on pain scores ($p=0.13$) nor was superiority observed on opioid consumption ($p=0.98$). Furthermore, no studies to date have compared TAP to EA in the specific setting of HPB surgery.

Enhanced Recovery (ER)

ER and fast-track protocols were initially implemented in the perioperative management of the surgical patient over 20 years ago. While ER originated in colorectal surgery, it has been broadly adapted to most surgical specialties, including the field of HPB. Although there are many common ER end points that are routinely measured and improved with its utilization (shortened length of stay, improved functional outcomes, and decreased costs),[28] one of the most critical is effective pain control. Patient education and engagement are the foundation of all ER programs. Moreover, a multi-disciplinary approach is necessary to support this foundation with four fundamental perioperative care principles that include: early feeding, early ambulation, goal directed fluid therapy, and opiate-sparing analgesia (Figure 4).[29]

ER protocols commonly have an opiate-sparing analgesia principle that is achieved through a multimodal approach. One of these components includes the consideration of nonsteroidal anti-inflammatory drugs, which are commonly utilized in our institution's ER liver surgery protocol. Use of NSAIDs have shown to reduce overall narcotic use, reduce postoperative nausea/vomiting, and accelerate time to flatus/discharge.[30] A meta-analysis of 22 prospective, randomized, double-blind studied including 2,307 patients showed NSAIDS to decrease postoperative nausea and vomiting by 30% and sedation by 29%.[31] Additional regression analysis demonstrated the incidence of nausea and vomiting was positively correlated with morphine consumption. However, one study observed that early administration of COX-2 inhibitors may be a risk factor for pancreatic fistula in patient who undergo PD.[32] In this study, use of non-selective inhibitors was not associated with an increase in PF, but COX-2 inhibitors were associated with increased pancreatic fistula (20.2% vs. 10.5%, p=0.033; OR 2.12, p=0.044).

A meta-analysis of all randomized trials comparing EA to an alternative analgesic technique following open abdominal surgery within an ER setting recently identified 7 studies from 1966 to 2013.[33] Overall, the analysis of 378 patients did not identify a difference in complication rate (OR 1.14 CI 0.49–2.64, p=0.76), but a sub analysis between PCA vs. EA showed a lower rate of complication (OR 1.97 CI 1.10–3.53, p=0.02) in patients who received an IV PCA. Although EA was associated with a faster return of gut function and reduced pain scores, no difference in length of stay was observed. The vast majority of these randomized controlled trials were conducted in patients undergoing colorectal surgery, while only one trial was in patients who underwent open hepatic resection.[20]

Additional high-level evidence regarding pain control is required in the context of ER for patients undergoing HPB surgery. Currently, the University of Texas MD Anderson Cancer Center is conducting a randomized clinical trial comparing TAP infiltration to EA in liver surgery patients in the setting of ER.

Patient-Reported Outcomes (PRO) and Return to Intended Oncologic Therapy (RIOT)

Adequate pain control is the most common primary patient-centric outcome that is assessed in studies comparing analgesic modalities after surgery. However, other outcomes of patient satisfaction or functional recovery are rarely measured in the vast majority of high-level studies. Now, there are validated PRO tools to measure these important outcomes in surgical patients.[34] The MD Anderson Symptom Inventory-GI is one example of a PRO tool that is composed of 24 questions broken into 3 sections (core, gastrointestinal, and symptom interference) used in gastrointestinal cancer patients to assess functional recovery (Figure 5).[35] Utilizing the MDASI-GI, Day et al. showed patients on an ER protocol after liver surgery was an independent predictor of return to baseline interference scores, a measure of functional recovery (OR 2.62 CI 1.15–5.94, p=0.021). These important validated tools should be utilized in the assessment of patient recovery when determining the optimal analgesic modality in HPB surgery.

Additional outcome measures to consider in the domain of perioperative analgesia is the analgesic modality's impact on a patient's ability to return to intended oncologic therapy (RIOT). Divided into 2 components: first, a binary outcome (whether the patient did or did not initiate intended oncologic therapies after surgery), and second, the time between surgery and the initiation of these therapies.[36] Intended "adjuvant" therapies encompassing the current multimodality state of cancer care, mandate beyond traditional adjuvant systemic therapy (ie. Second-stage operations, interventional radiology, endoscopic cancer therapies, radiotherapy, biological and hormonal therapies, etc). Implementation of the ER protocol at MD Anderson Cancer Center improved the rate of RIOT from 75% to 95% as well as a shorter time from 60.2 days to 44.7 days.[35] These data suggest the clinical importance for establishing a paradigm for the association of perioperative medical care with long-term oncologic outcomes and this measure of cancer care delivery should be included in the assessment of analgesic modalities in HPB surgery.

Summary

Currently, EA is supported by high-level evidence, specifically in liver surgery, to be the most effective analgesic modality for pain control after HPB surgery. Additional high-level evidence for superior analgesic modalities after pancreatectomies is required. Subsequent randomized controlled trials are required to elucidate the effectiveness and safety of new strategies such as a TAP block compared to EA for both hepatectomies and pancreatectomies in the setting of ER. Beyond adequate pain control and total opiate consumption, PRO tools and the ability to RIOT in cancer patients should be secondary outcome measure in all future studies.

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Key Points

- The vast majority of hepato-pancreato-biliary (HPB) surgery continues to be performed through an open approach, and the best modality to obtain adequate pain control continues to be a challenge.
- Currently, epidural analgesia is the most supported analgesic modality by high-level evidence (randomized clinical trials in liver surgery) for pain control, patient satisfaction, and minimization of total opiate use after HPB surgery.
- Historic concerns for analgesia-related events from epidural analgesia have not been observed in the most recent high-level studies.
- Randomized clinical trials comparing newer analgesic modalities (ie. Transversus Abdominis Plane infiltration) vs. Epidural Analgesia in the modern setting of Enhance Recovery protocols after HPB surgery are currently on going.

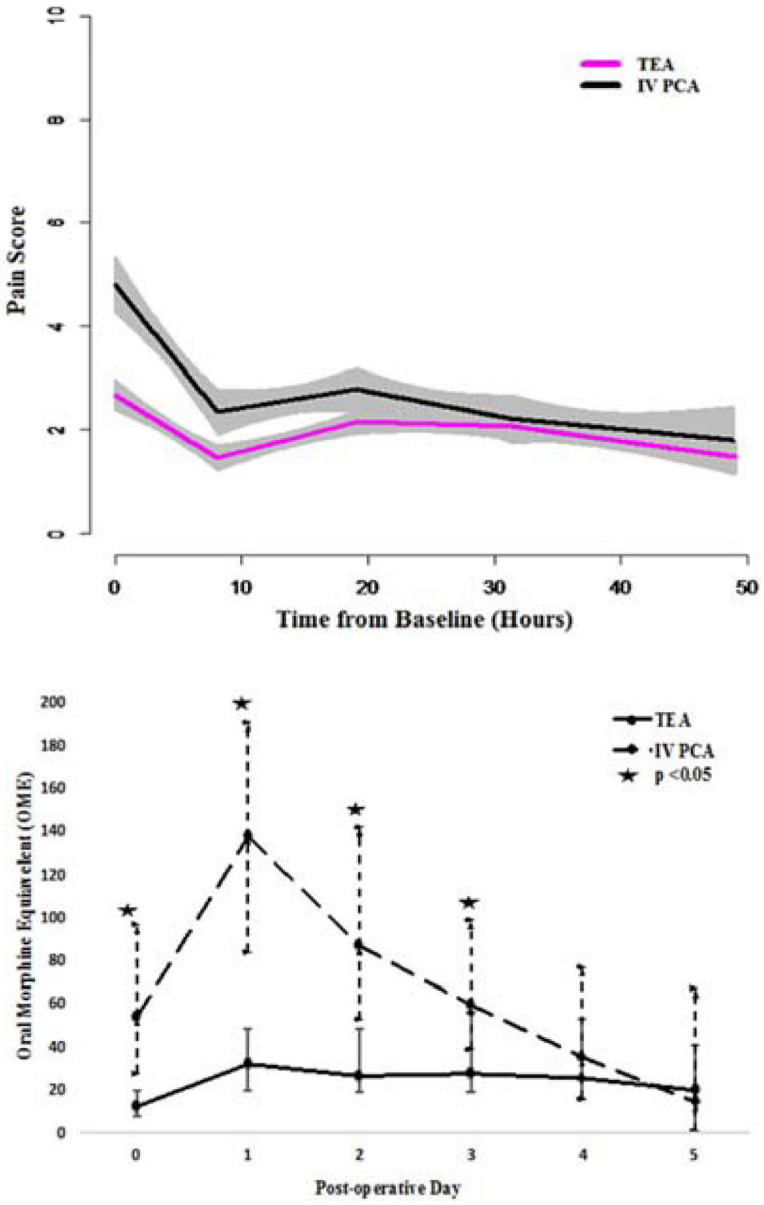

Figure 1.

A) Pain scores over time in thoracic epidural analgesia (TEA) versus intravenous patient controlled (IV PCA). B) Median oral morphine equivalent (with interquartile range) used on each postoperative day in TEA versus IV PCA.

From Aloia TA, Kim BJ, Segraves-Chun YS, et al. A Randomized Controlled Trial of Postoperative Thoracic Epidural Analgesia Versus Intravenous Patient-controlled Analgesia After Major Hepatopancreatobiliary Surgery. *Ann Surg* 2017;266;3;545–554, with permission.

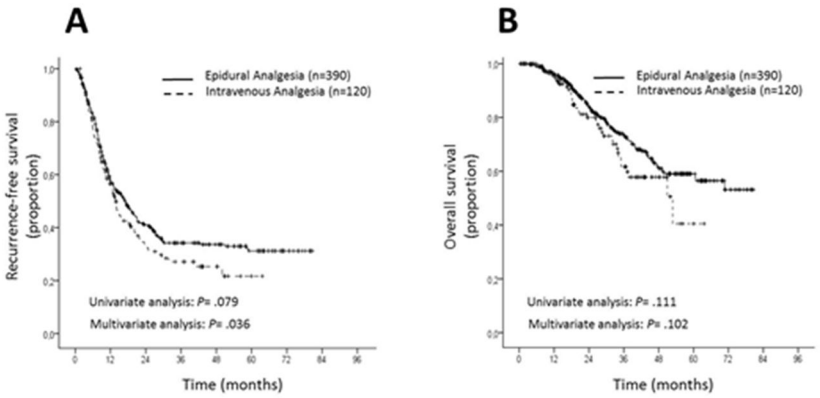

Figure 2.

Impact of analgesia type on recurrence-free survival (A) and overall survival (B).

From Zimmitti G, Soliz J, Aloia TA, et al. Positive Impact of Epidural Analgesia on Oncologic Outcomes in Patients Undergoing Resection of Colorectal Liver Metastases. *Ann Surg Oncol* 2016;23;3;1003–1011, with permission

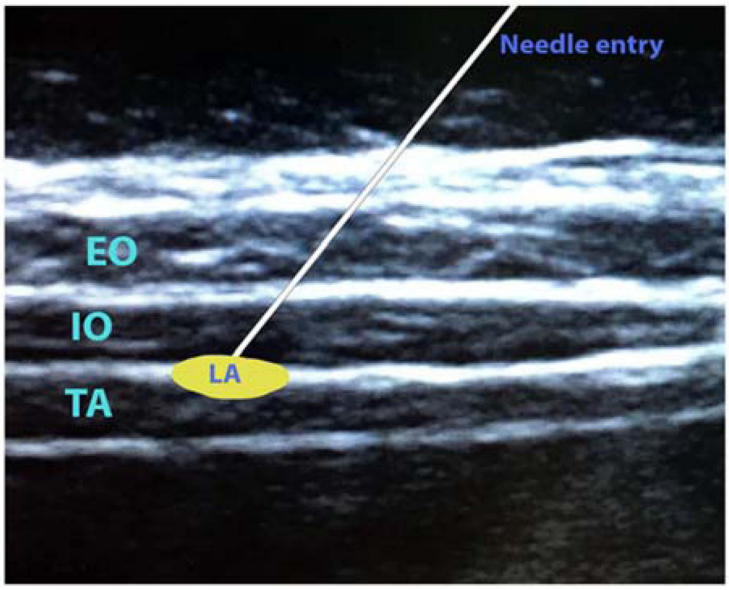

Figure 3.
Ultrasound image of tranverse abdominis plane block. EO: external oblique muscle, IO: internal oblique muscle, TA: transverse abdominis muscle, LA: local anesthetic

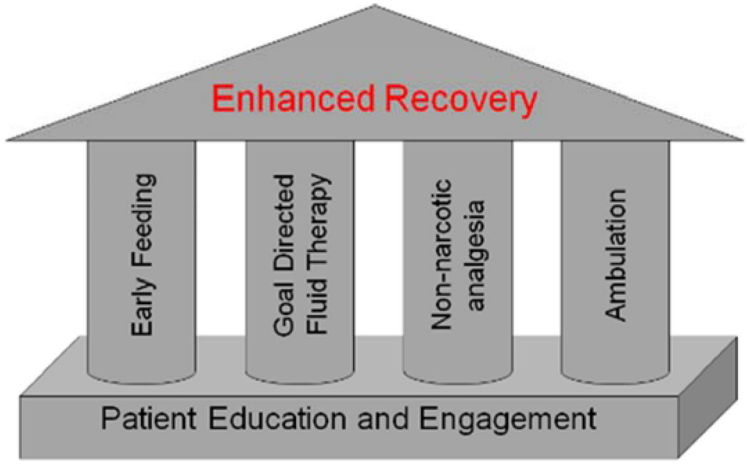

Figure 4.

Enhanced Recovery sits on a foundation of patient education and engagement. Four perioperative fundamental strategies that support the program are early feeding, goal directed fluid therapy, multimodal opiate limited analgesia, and ambulation.

From Kim BJ, Aloia TA. What Is "Enhanced Recovery," and How Can I Do It? J Gastro Surg 2017;22;164–171; with permission.

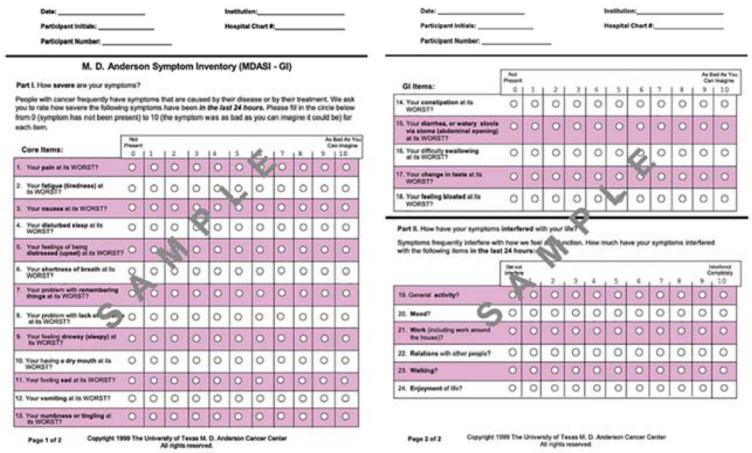

Figure 5.

University of Texas MD Anderson Symptom Inventory (MDASI)-Gastrointestinal. A validated Patient-Reported Outcome tool.

From Day RW, Cleeland CS, Wang XS, et al. Patient-Reported Outcomes Accurately Measure the Value of an Enhanced Recovery Program in Liver Surgery. *Journal American College of Surgeons.* 2015;221;6;1023–1030 e1021–1022, with permission.