A Prospective, Randomized, Double-Blind, Placebo Controlled Trial on the Efficacy of Ethanol Celiac Plexus Neurolysis in Patients with Operable Pancreatic and Periampullary Adenocarcinoma

Harish Lavu, MD, FACS, Harry B Lengel, BA, Naomi M Sell, BA, Joseph A Baiocco, BS, Eugene P Kennedy, MD, FACS, Theresa P Yeo, PhD, Sherry A Burrell, PhD, Jordan M Winter, MD, FACS, Sarah Hegarty, MPhil, Benjamin E Leiby, PhD, Charles J Yeo, MD, FACS

BACKGROUND: Ethanol celiac plexus neurolysis (ECPN) has been shown to be effective in reducing cancer-related pain in patients with locally advanced pancreatic and periampullary adenocarcinoma (PPA). This study examined its efficacy in patients undergoing PPA resection.

STUDY DESIGN: There were 485 patients who participated in this prospective, randomized, double-blind placebo controlled trial. Patients were stratified by preoperative pain and disease resectability. They received either ECPN (50% ethanol) or 0.9% normal saline placebo control. The primary endpoint was short- and long-term pain and secondary endpoints included postoperative morbidity, quality of life, and overall survival.

RESULTS: Data from 467 patients were analyzed. The primary endpoint, the percentage of PPA patients experiencing a worsening of pain compared with preoperative baseline for resectable patients, was not different between the ethanol and saline groups in either the resectable/pain stratum (22% vs 18%, relative risk [RR] 1.23 [0.34, 4.46]), or the resectable/no pain stratum (37% vs 34%, RR 1.10 [0.67, 1.81]). In multivariable analysis of resected pancreatic ductal adenocarcinoma (PDA) patients, there was a significant reduction in pain in the resectable/pain group, suggesting that surgical resection of the malignancy alone (independent of ECPN) decreases pain to a significant degree.

CONCLUSIONS: In this study, we demonstrated a significant reduction in pain after surgical resection of PPA. However, the addition of ECPN did not synergize to result in a further reduction in pain, and in fact, its effect may have been masked by surgical resection. Given this, we cannot recommend the use of ECPN to mitigate cancer-related pain in resectable PPA patients. (J Am Coll Surg 2015;220:497−508. © 2015 by the American College of Surgeons)

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer death in the United States, with an expected 46,420 new cases and 39,590 deaths in 2014.[1] Surgical resection is the only potentially curative therapy.[2] Unfortunately, at the time of diagnosis, the majority of patients are ineligible for tumor resection primarily due to the presence of locally advanced disease, distant metastasis, or significant medical comorbidities precluding surgery.[3-6] The 5-year survival rate for all patients with PDA is 6% and improves to 15% to 25% in patients who undergo surgical resection.[5,7-11] Treatment strategies used for PDA are similar to those for ampullary adenocarcinoma, distal

Disclosure Information: Nothing to disclose.

Support: Statistical analysis funded by the Kimmel Cancer Center core grant (5 P30 CA056036-10 and 5 P30 CA056036-16). ClinicalTrials.gov number, NCT00806611.

Presented at the Southern Surgical Association 126th Annual Meeting, Palm Beach, FL, November 30−December 3, 2014.

Received December 7, 2014; Accepted December 9, 2014.

From the Department of Surgery (Lavu, Lengel, Sell, Baiocco, Kennedy, TP Yeo, Winter, CJ Yeo) and Division of Biostatistics (Hegarty, Leiby), Thomas Jefferson University, Jefferson Pancreas Biliary and Related Cancer Center, Philadelphia, PA and the School of Nursing, Rutgers University, The State University of New Jersey, Camden, NJ (Burrell).

Correspondence address: Harish Lavu, MD, FACS, Thomas Jefferson University, 1025 Walnut St, Suite 605, Philadelphia, PA, 19107. email: harish.lavu@jefferson.edu

http://dx.doi.org/10.1016/j.jamcollsurg.2014.12.013
ISSN 1072-7515/14

Abbreviations and Acronyms

BPI = Brief Pain Inventory
ECPN = ethanol celiac plexus neurolysis
PDA = pancreatic ductal adenocarcinoma
PPA = pancreatic and periampullary adenocarcinoma
QOL = quality of life
R/NP = resectable with no pain
R/P = resectable with pain
RR = relative risk
UR/NP = unresectable with no pain
UR/P = unresectable with pain

cholangiocarcinoma, and duodenal adenocarcinoma, which are the other major cancers that occur within the periampullary region. Taken together, pancreatic and periampullary adenocarcinoma (PPA) present significant clinical challenges for achieving long-term survival in afflicted patients, and therefore, adjunctive and palliative therapies are extremely important in alleviating patient suffering.

Abdominal and back pain are among the most common presenting symptoms in patients with PPA, estimated to affect 30% to 40% of patients at the time of diagnosis.[12] Even in those patients who initially do not present with pain, the majority will ultimately develop this symptom during the course of their disease.[13,14] Pain associated with PPA is typically unremitting, located in the epigastrium, and can intensify as the disease progresses.[13,15] Other symptoms associated with and known to cluster with this type of pain include fatigue, insomnia, nausea, diarrhea, weight loss, anxiety, and depression.[16,17] These symptoms have been documented to have a significant negative impact on patient quality of life (QOL).[4,17,18] Current recommendations suggest that the most effective approach to cancer-related pain treatment involves using systemic medications titrated in a progressive manner, starting with nonopioid analgesics, moving to weak opioids, and then to strong opioids depending on pain intensity.[19,20] Although opioids can effectively achieve pain relief, they are associated with many adverse side effects. Therefore, nonpharmacologic adjuncts, such as ethanol celiac plexus neurolysis (ECPN), have been used in order to offer effective pain relief while minimizing drug-related side effects.

Despite the first description of celiac plexus neurolysis by Kappis in 1914, clear and convincing evidence supporting the routine use of ECPN in the management of PPA pain is lacking.[21,22] The most complete study evaluating this topic was published by Lillemoe and associates[23] in 1993. This study investigated the efficacy of ECPN in PPA patients found to be unresectable during surgical exploration, demonstrating a significant reduction in pain and an improvement in survival in a small subset of patients with preoperative pain. Subsequent studies have also suggested an improvement in pain in patients with unresectable PPA who have undergone ECPN.[6,24-31] Despite this strong evidence supporting the use of ECPN in patients with unresectable PPA, no studies to date have evaluated the role of ECPN in patients with resectable PPA. The question remains whether ECPN can be equally effective in reducing PPA-associated pain after surgical resection, and if this will result in an improvement in patient QOL. There is also the question of the theoretic antitumor effect of ablating nerves that are infiltrated by malignant cells, which could be hypothesized to exert an influence on cancer recurrence rates and overall survival.

In this trial, we sought to test the hypothesis that intraoperative ECPN would be beneficial for patients with resectable PPA. The primary objective was to evaluate whether ECPN would affect short- and long-term tumor-related pain; secondary endpoints included perioperative complications, QOL, and overall survival.

METHODS

Trial design

We performed a single-center, prospective, randomized, double-blind placebo controlled trial to evaluate the role of ECPN in mitigating cancer-associated pain in patients with resectable PPA. The trial was approved by both the Jefferson Clinical Cancer Research Review Committee and the Institutional Review Board and is registered with ClinicalTrials.gov (NCT00806611). From December 2008 to August 2013, patients undergoing abdominal exploration for presumed periampullary malignancy at the Thomas Jefferson University Hospital (TJUH) were offered participation in the study. All patients over 18 years old requiring major abdominal surgery for PPA were eligible for enrollment, with the exclusion of patients not found to have adenocarcinoma on the final pathology and those who had received a previous, preoperative celiac plexus nerve block. At the initial outpatient office visit and after education about the study, informed consent was obtained and patients filled out surveys of preoperative baseline pain (Brief Pain Inventory [BPI]) and QOL (Functional Assessment of Cancer Therapy - Hepatobiliary [FACT-Hep], version 4).

Patients believed to harbor resectable PPA underwent exploratory laparotomy with confirmation of tumor resectability. If, in fact, the cancer was determined to be resectable (as preoperatively assessed), either pancreaticoduodenectomy or distal pancreatectomy with en-bloc