Pain Physician 2016; 19:281-292 • ISSN 1533-3159

Retrospective Evaluation

The Effectiveness of Alcohol Versus Phenol Based Splanchnic Nerve Neurolysis for the Treatment of Intra-Abdominal Cancer Pain

Dhanalakshmi Koyyalagunta, MD, Mitchell P. Engle, MD, PhD, Jun Yu, Lei Feng, and Diane M. Novy, PhD

From: MD Anderson Cancer Center, Houston, TX

Address Correspondence:
Dhanalakshmi Koyyalagunta, Md
MD Anderson Cancer Center
1400 Holcombe Blvd
Unit 409
Houston, TX
E-mail:
dkoyyala@mdanderson.org

Disclaimer: This work was supported in part by the Cancer Center Support Grant (CCSG) (NCI Grant P30 CA016672).

Manuscript received: 12-03-2014
Revised manuscript received: 09-14-2015, 12-16-2015
Accepted for publication: 12-17-2015

Free full manuscript:
www.painphysicianjournal.com

Pancreatic and other upper abdominal organ malignancies can produce intense visceral pain syndromes that are frequently treated with splanchnic nerve neurolysis (SNN) or celiac plexus neurolysis (CPN). Although commonly performed with either alcohol or phenol, there is scant literature on the comparative effectiveness, duration of benefit, and complication profile comparing the 2 agents. This study presents a retrospective chart review of 93 patients who underwent SNN for cancer-related abdominal pain in order to describe patient characteristics, examine comparative efficacy, duration of benefit, and incidence of complications with alcohol vs. those of phenol. Consistent with previous studies, SNN reduced reported pain scores while not significantly reducing opioid consumption. No difference in pain outcomes was found comparing alcohol versus phenol based neurolytic techniques. Celiac axis tumor infiltration and pre-procedural local radiation therapy did not change the effectiveness of the procedure. Our data demonstrated that 44.57% of patients had ≥ 30% pain reduction while 43.54% did not have pain reduction. Interestingly, the procedure produced significant improvements in anxiety, depression, difficulty thinking clearly, and feeling of well-being. In addition, no difference in complications was seen between the agents either. SNN was an effective and relatively safe procedure for the treatment of pain associated with pancreatic and other upper abdominal organ malignancies in our sample of patients. Choice of neurolytic agent can appropriately be left to the clinical judgment and local availability of the treating physician. The change in ancillary symptoms has a theoretical basis that supports a biopsychosocial model of pain since changes in one target area (pain) impact other related ones (depression and anxiety).

Key words: Celiac plexus, splanchnic nerves, neurolysis, nerve block, alcohol, ethanol, phenol, pain, cancer pain, abdominal pain, visceral pain, symptom assessment

Pain Physician 2016; 19:281-292

Malignancy related abdominal and pelvic pain can be debilitating and affects survival as well as quality of life (1). The prevalence of cancer pain is 59% with gastrointestinal malignancies, 52% with urogenital malignancies, and 60% with gynecological malignancies (2). Abdominal pain may be tumor related from stretching, compression, invasion, or distension of the visceral structures, or could be treatment-related secondary to tissue injury from radiation or surgery. Patients typically describe the pain as deep, crampy, colicky in nature. Pancreatic adenocarcinoma is an aggressive tumor and is the fourth leading cause of cancer deaths in the United States (3). Most patients with pancreatic cancer present with advanced disease that is not surgically resectable and have a poor prognosis. Pain associated with pancreatic cancer is typically localized to the epigastric area radiating to the back. Frank involvement of the celiac plexus, typically by a pancreatic mass and or lymph nodes, remains another known etiology of epigastric pain (4). The celiac plexus is the largest visceral plexus comprising of a dense network of fibers from the celiac, superior mesenteric, and aorticorenal ganglia. It lies in the retroperitoneal space anterior

to the diaphragmatic crus and inferior to the celiac artery origin. The sympathetic nerves supplying the liver, pancreas, gall bladder, stomach, spleen, kidneys, adrenal glands, and part of the intestine (from the gastroesophageal junction to the splenic flexure of the colon) originate in the intermediolateral nucleus in the spinal cord, pass through the paravertebral sympathetic chain, form the splanchnic nerves, and then synapse in the celiac plexus. Visceral afferent fibers follow along the same sympathetic efferent pathways outside of the spinal cord. As such, visceral pain arising from tumors of these organs can be alleviated by a celiac plexus or splanchnic nerve block.

A strong association between cancer pain and distress is evident across the disease spectrum (5,6). The inherent uncertainty of cancer, and also of the duration of pain, can intensify the pain experience and increase emotional distress. Psychological disorders are twice as prevalent among cancer patients with pain as those without. Pain from cancer and its treatments can result in anxiety, depression, fear, anger, helplessness, and hopelessness, and those with both pain and depression have an amplification of disability and poor quality of life (6,7). Cancer pain affects many facets of the individual's social support, as higher levels of pain are associated with decreased social activities, lower levels of social support, reduced social functioning, and lower resiliency of the social network (6,8). Individuals with heightened cancer pain have a greater tendency to cope through catastrophizing (6,9). Cancer pain differs from chronic non-cancer pain, as a cancer diagnosis is linked with death, uncertainty, and loss of control (5,10). The pain experience and level of suffering related to a cancer diagnosis, cancer pain or treatment side effects can be heightened by high levels of depression and anxiety. For example, anxiety and tension can heighten sympathetic nervous system activity, which can lead to muscle spasm, vasoconstriction, and other physiological changes. These changes have the potential to decrease pain tolerance, to worsen the pain experience, and to increase total suffering (11). Given the complex interaction of disease process and pain, as well as the potential for significant psychological symptom burden, pain relief from any modality of treatment has the ability to reduce not only physical pain but also related symptoms of depression and anxiety.

Although many patients with cancer adjust to the stress of the disease and its symptoms without a diagnosable psychological disorder, a significantly higher rate of depression and anxiety symptoms are found among cancer patients with higher levels of pain than those with lower levels (12). In general however, depression and anxiety are among the most common psychological symptoms experienced by cancer patients (13-15). The etiology of psychological symptoms in cancer patients, both with and without pain, are diverse and range from reactions to the diagnosis of cancer, concerns of disease recurrence or progression, diminished quality of life, interruptions with life plans, and pre-existing psychological dysfunction. Psychological distress can also arise in cancer patients in response to treatments, adverse disease symptoms, and/or treatment side effects. For example, cancer treatments often provide ample opportunity for anticipatory anxiety. Patients may worry about the next check-up, procedure, reaction to chemotherapy and/or radiation, test results, the cause of new or different pain, etc. Empirical evidence has demonstrated that the presence of depression is associated with the amplification of the experience of pain (16).

Given the co-occurrence of cancer symptoms and known biopsychosocial interrelations in cancer pain, it seems natural that interventions (e.g., blocks) that target one symptom (e.g., pain) may also have a positive effect on other symptoms (e.g., depression and or anxiety). If, for example, a person is experiencing a high degree of depression and anxiety related to cancer pain, then you would expect that treatment aimed to assist the patient in finding ways to cope with and manage the pain would also help to improve the psychological symptoms of depression and anxiety (17). Among patients with advanced pancreatic cancer, promoting quality of life has been identified as an important treatment goal. The complex symptom burden, including impaired sense of well-being and pain, have been found to improve with palliative chemotherapy for such patients (18).

Neurolytic blocks are a mainstay in the armamentarium of cancer pain management, particularly with intractable pain from advanced cancer. These procedures may be performed using either phenol or alcohol to disrupt transmission of pain signals via Wallerian degeneration distal to the lesion. Radiofrequency ablation of the splanchnic nerves is an option, though infrequently done in cancer pain. The complication rate from celiac plexus neurolysis (CPN) or splanchnic nerve neurolysis (SNN) with either treatment is low, estimated to be 1 – 2% (6). The most commonly experienced side effects are hypotension, increased defeca-

tion, and backache. However, the potential for severe complications such as neuritis, retroperitoneal bleeding, urinary retention, and serious neurologic compromise including paraplegia, often preclude non-cancer patients from receiving CPN or SNN. Since CPN and SNN have historically been thought to reduce cancer pain burden with relatively infrequent significant complications, these techniques have gained widespread acceptance (19). The agents currently used for chemical neurolysis are alcohol (50% – 100%) or phenol (5% – 10%), and they produce a block that lasts 3 – 6 months (20,21). Alcohol acts by denaturing proteins, fatty substance extraction, and precipitation of the lipoproteins and mucoproteins (22), damaging both the Schwann and nerve cells resulting in Wallerian degeneration. Alcohol is intensely painful upon injection. It is hypobaric, water soluble, and spreads rapidly from the injected site. Consequently, larger volumes are required in comparison to phenol. Alcohol may also be associated with a higher rate of neuritis than phenol (19). Phenol is primarily a local anesthetic at lower concentrations and becomes more neurolytic at higher concentration. Unlike alcohol, it is not painful on injection. It is prepared in a mixture with glycerin in which it is highly soluble and hyperbaric. In a mixture with glycerin it diffuses slowly into the local tissues. Aqueous mixtures of phenol are more potent neurolytic agents and can be used as well. Phenol diffuses into the axon and perineural blood vessels and denatures proteins causing Wallerian degeneration with a relative sparing effect on the dorsal root ganglia (23). Although phenol might yield a lower risk of neuritis, there is a question as to how it relates in intensity and extent of treatment effect compared to alcohol. There is scant literature on the comparative effectiveness, duration of benefit, and complication profile comparing the 2 agents. There is one study comparing alcohol to phenol in motor branch neurolysis of the tibial nerve for spasticity management post stroke (24). However, there are no studies comparing these neurolytic agents or their risk, benefit, or effectiveness profiles in SNN.

The purpose of this study was to determine the relative effectiveness of alcohol versus phenol used during SNN for pain related to upper abdominal malignancies. The primary end point was pain reduction at one month and 6 months. Secondary endpoints were ancillary symptom changes as assessed by the Edmonton Symptom Assessment Scale (ESAS), morphine equivalent daily dose changes, and complications (26).

Methods

This study was approved by the institutional review board at the University of Texas MD Anderson Cancer Center. Waivers of informed consent and authorization were not necessary because this was a retrospective study that did not involve new diagnostic or therapeutic interventions or direct patient contact. A thorough chart review was conducted on all patients who underwent CPN or SNN from July 15, 2007, to July 14, 2010, a period spanning 3 years. Study candidates were identified by searching the operating and procedure room schedules. A HIPAA compliant database was created on Filemaker Pro version 9. The data initially identified 99 patients. Of these, 28 patients were treated with alcohol and 71 patients were treated with phenol. Five patients who did not undergo the procedure for upper abdominal malignancies were excluded from the analysis. One patient who had CPN was excluded from the analysis to make it a uniform sample. Demographic data were collected on all patients and included age, gender, medical history, categorized by cancer diagnosis, active cancer vs. remission, extent of cancer, pain medications, chemotherapy, and radiation. Institutional databases (clinic and operating room notes) were used to collect these data. Prior to neurolysis and at subsequent visits, patients rated their pain using the Brief Pain Inventory (BPI) (25) and reported the severity of their other symptoms using the ESAS (26). Collected peri-procedural data included technique of block, use of alcohol vs. phenol, volume of agent used, radiation prior to block, and celiac plexus tumor involvement (all radiology reports were reviewed for nodal involvement of celiac axis prior to procedure). Post-procedure data were collected from clinic notes and included BPI, ESAS, hypotension, increased defecation, neuritis, pneumothorax, and other adverse reactions. Two time points were selected for analysis. The first time point occurred within one month of the procedure at the subsequent outpatient follow-up or phone conversation. The second time point, for which much fewer data points could be obtained, was derived from outpatient clinic visit notes from 2 to 6 months after the procedure.

Descriptive statistics including mean, standard deviation, median, and range for continuous variables were calculated; frequency counts and percentages for categorical variables, such as gender, cancer diagnosis, and treatment were reported. Wilcoxon signed rank test was used to compare if the change in score measurements between time points is different from zero.

Fisher's exact test or Chi-square test was used to evaluate the association between 2 categorical variables. Wilcoxon rank sum test or Kruskal-Wallis test was used to evaluate the difference in a continuous variable between/among patient groups. Statistical software SAS 9.1.3 (SAS, Cary, NC) was used for all analyses.

Table 1. *Demographic information*.

	Frequency	Percentage
Gender		
Female	47	50.0
Male	47	50.0
Cancer Type		
Pancreatic	54	54.3
Es, Ga, HB, Sp, Du, Ad*	21	22.3
Met to Abdomen	22	23.4
Cancer Status		
Active Cancer	89	94.7
Remission	2	2.1
Not Documented	3	3.2
Celiac Axis Disease		
Yes	28	29.8
No	66	70.2
Prior Chemotherapy		
Yes	75	79.8
No	19	20.2
Prior Radiation Therapy		
Yes	24	25.5
No	70	74.5
Neurolytic Agent		
Alcohol	27	28.7
Phenol	67	71.3
Procedure Type **		
CP Neurolysis	1	1.1
SN Neurolysis	93	98.9
Anatomical Level		
T11	3	3.2
T12	85	90.4
L1	5	5.3
L2	1	1.0
Laterality		
Unilateral	2	2.1
Bilateral	92	97.9

* Es (esophagus), Ga (gastric), HB (hepatobiliary), Sp (Splenic), Du (Duodenal), Ad (Adrenal).
** CP (celiac plexus), SN (splanchnic nerve).

Results

Demographic Data

A total of 93 patients underwent SNN for cancer related pain during the study period. Two patients had a repeat block within the analysis period (6 month period). Data shown reflects all patients as there was no difference in the results when these 2 patients were excluded from the analysis. All procedures were performed for pain secondary to pancreatic cancer (53.76%), esophageal, gastric, hepatobiliary, splenic, duodenal, or adrenal cancers (combined 22.58%), or metastatic disease to the abdomen (23.66%) (Table 1). Almost all (97.78 %) of the patients had active cancer and 79.57% of them had undergone chemotherapy prior to the procedure. Regional radiation therapy was performed prior to or concurrent with the procedure in 26.88% of the cases. Tumor infiltration of the celiac axis was present in 29.03% of the cases. Phenol (10% phenol in 20% glycerin) was used in 72.04% of cases while alcohol (98% dehydrated ethanol) was used in the remaining 27.96% of cases. The procedure was most commonly performed at the T12 vertebral level. A few patients with metastatic disease had concurrent superior hypogastric plexus neurolysis performed at the L5/S1 level. The average numeric pain score prior to the procedure was 5.1 ± 2.2 on an 11 point scale. The average morphine equivalents daily dose (MEDD) prior to the procedure was 230.09 mg ± 205.08 mg.

Overall Effects of Neurolysis

Comparing pre-procedure and one month post-procedure, SNN produced an average pain reduction of 1.17 ± 2.77 (median -1 [range -10, 5]) on an 11 point numeric pain scale (P = 0.0001; Fig. 1). In addition, using the ESAS, after the procedure the depression score reduced by 0.85 ± 2.68 (0 [-7, 5], P = 0.0208), anxiety score reduced by 1.06 ± 2.59 (-1 [-8, 5], P = 0.0015), and difficulty thinking clearly score reduced by 0.98 ± 2.89 (0 [-9, 7], P = 0.0144) at one month. Also, feeling of well-being trended towards improvement by 0.83 ± 3.10 (0 [-8, 6], P = 0.0749). Conversely, on average shortness of breath worsened by 1.14 ± 3.12 (0 [-6, 10], P = 0.0037). After the procedure, there was no significant change in the fatigue, nausea, drowsiness, poor appetite, or insomnia scores. (Fig. 1). Importantly, the change in morphine equivalent dose utilization at one month

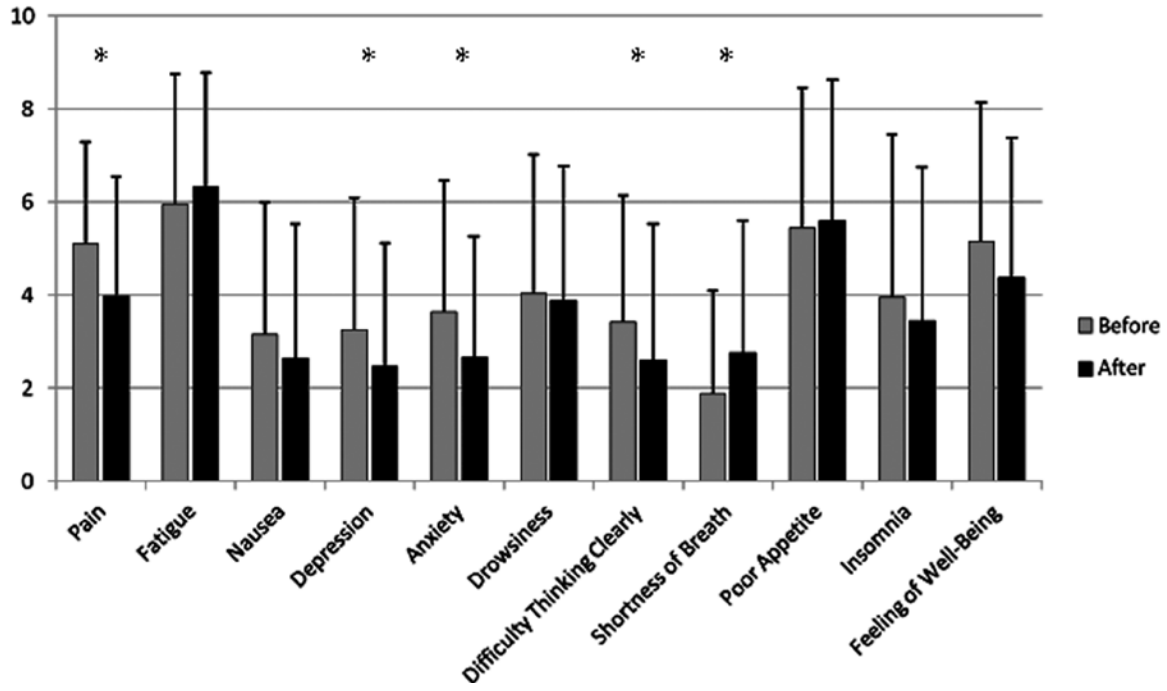

Fig. 1. *Splanchnic nerve neurolysis (SNN) or celiac plexus neurolysis (CPN) impact pain and symptom burden. Bar chart of the numeric pain scores (NPS) and Edmonton Symptom Assessment Scores (ESAS) before and one month after SNN or CPN. The NPS and ESAS both utilize an 11-point scoring system with 0 indicating no symptom and 10 indicating the most severe symptom. Mean ± S.D. * P < 0.05.*

was reduced but this change was not significant (-38.32 mg ± 230.24 mg, -10 [-960, 725]; *P* = 0.1403). The effects of neurolysis on pain scores and ESAS components were documented in less than a third of the patients by the second time point out to 6 months. In general, pain and symptom burden (ESAS) were lower except for shortness of breath. However, the changes were not statistically significant.

Effect of Alcohol Versus Phenol

Using a Wilcoxon rank sum tests, one month post-procedure pain scores were not different between those treated with alcohol (4.23 ± 2.69, 4 [1, 9]) versus phenol (3.87 ± 2.53, 4 [0, 10]; *P* = 0.66). In addition, ESASs and MEDD were not significantly different either (Fig. 2).

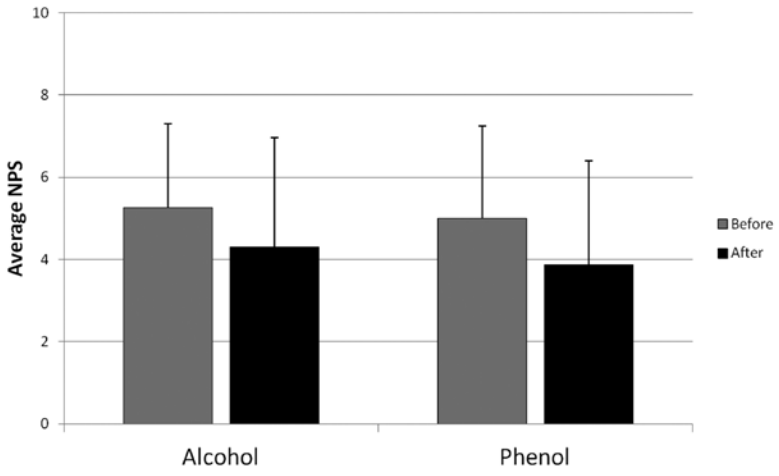

Fig. 2. *Alcohol and phenol equally reduce numeric pain score (NPS) after either splanchnic nerve neurolysis (SNN) or celiac plexus neurolysis (CPN). Bar chart of the numeric pain scores (NPS) before and one month after SNN or CPN with either alcohol or phenol. Both alcohol and phenol produced a significant reduction in NPS. However, no difference in pain reduction was present when comparing alcohol with phenol. Mean ± S.D. * P < 0.05. N.S. Not Significant.*

There was a small difference in the volume of neurolytic agent used between the 2 agents with 24.73 ± 8.89 mL (20 [10, 50]) used for alcohol and 20.24 ± 5.05 mL (20 [10, 30]) used for phenol (P = 0.0044).

Effect of Celiac Axis Involvement

Pancreatic cancer had a higher percentage of celiac axis tumor involvement (24/50; 48%) than the other upper abdominal cancers or metastases (3/43; 7%; P < 0.0001). The difference in the following variables between the presence of celiac axis involvement and the absence of celiac axis involvement was not significant: effectiveness of neurolysis for pain reduction (P = 0.1301), ESAS items change, or MEDD change (P = 0.88).

Table 2. *Responder analysis at 1 month.*

Pain Reduction	Number	Percentage
30% Pain Reduction Threshold		
≥30%	41	44%
1-29%	11	12%
No Reduction	41	44%
50% Pain Reduction Threshold		
≥50%	29	31%
1-49%	23	25%
No Reduction	41	44%
70% Pain Reduction Threshold		
≥70%	16	17%
1-69%	36	39%
No Reduction	41	44%

Effect of Pre-Procedural Local Radiation Therapy

A total of 23 patients had local radiation therapy prior to the neurolytic procedure. The most common diagnosis that received radiation therapy was pancreatic cancer (16/23; 69.6%; P = 0.0322). In addition, patients who had pre-procedural radiation were more likely to have pre-procedural chemotherapy than patients without pre-procedural radiation therapy (95.7% vs. 74.3%; P = 0.0351). The difference in pain reduction (P = 0.15), ESAS items, or MEDD (P = 0.179) at one month between the pre-procedural radiated group and non-radiated group was not significant. At the second clinical data point, pre-procedural radiation therapy was associated with worse fatigue (P = 0.016) and appetite (P = 0.066).

Effect of Cancer Type

For this analysis, abdominal cancer was divided into 3 groups: 1. pancreatic cancer; 2. upper abdominal cancers such as esophageal, gastric, hepatobiliary, splenic, duodenal, and adrenal; and 3. metastasis to the abdomen. Pancreatic cancer was more common in men than women (63.8% vs. 43.5%) while metastatic disease to the abdomen was more common in women than men (34.8% vs. 12.8%) (P = 0.0372). Pre-procedural radiation therapy was more common for pancreatic and upper abdominal cancers than for metastatic disease (P = 0.0129). A Kruskal-Wallis test was used to evaluate the difference in variables among patients with different cancer types. No significant difference was found in MEDD among cancer types. In addition, the pain score change at one month was similar between pancreatic cancer (-1.14 ± 2.63, -1 [-8, 5]), upper abdominal cancer (-0.9 ± 2.43, -1 [-5, 4]), and abdominal metastatic disease (-1.48 ± 3.42, -1 [-10, 4]) related pain (P = 0.92).

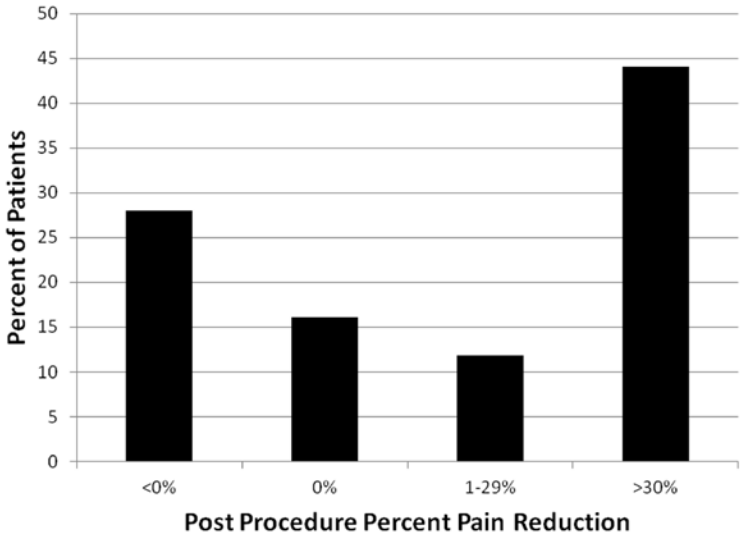

Fig. 3. Splanchnic nerve neurolysis (SNN) or celiac plexus neurolysis (CPN) produce a binomial distribution of reduction in numeric pain scores (NPS). Responder analysis histogram of percent of patients achieving designated responses to either SNN or CPN.

No significant difference in change in ESAS items was found among the different types of cancer.

Pain Reduction Responder Analysis

An analysis was conducted to assess frequency on degree of pain reduction response to SNN. The pain reduction thresholds for positive responses were set at 30%, 50%, and 70%. Greater than or equal to 30%, 50%, and 70% pain reduction was present in 44.57%, 31.52%, and 17.39% of the patients, respectively (Table 2; Fig. 3). The average percent pain relief for patients with greater than or equal to 30% relief was a 64% reduction. The average pain change for these patients (n = 41) was -3.57 ± 1.81,-3 (-10, -1). Interestingly, 43.54% of the patients had either unchanged or worsened pain after the procedure. There was no difference in the rate of response between the patients who had alcohol vs. phenol neurolysis.

Complications

Two patients had symptomatic hypotension that was treated with intravenous fluids. One patient who had a concomitant superior hypogastric plexus and complained of left leg weakness post-procedure which was attributed to progression of disease with left groin lymphadenopathy vs. neurolytic agent tracking along the iliopsoas muscle. Motor strength was at a 4/5 in the left hip vs. 5/5 on the right. Another patient was evaluated in the emergency room for shortness of breath after the procedure. Computed tomography (CT) of the chest revealed progression of disease in the lungs, no pneumothorax.

Discussion

The celiac plexus is a diffuse network of nerve fibers and ganglia (1-5) at the level of T12/L1 to L2 on the anterolateral surface of the aorta. It is the largest visceral plexus and comprises a dense network of interconnecting nerve fibers from the celiac, superior mesenteric, and aorticorenal ganglia. It is a retroperitoneal structure and lies anterior to the crus of the diaphragm and inferior to the celiac artery origin. The relationship to the celiac artery is relatively consistent and a reliable landmark for localizing the celiac plexus when using CT or ultrasound guidance. Sympathetic innervation to the abdominal viscera arises from preganglionic fibers from T5-T12 via the ventral roots. These roots unite to form the greater, lesser, and least splanchnic nerves which traverse through the diaphragmatic crus to synapse at the celiac plexus. Visceral afferents from the lower esophagus, stomach, pancreas, liver, gall bladder, and parts of the intestine up to the splenic flexure transmit sensory information through the splanchnic nerves and celiac plexus.

Patient Selection and Indications

Patients with cancer involving the lower esophagus, stomach, pancreas, liver, gall bladder, and parts of the intestines up to the splenic flexure present with upper abdominal pain with occasional radiation to the back, and intractable pain not relieved with opioids or medication related side effects are ideal candidates for a CPN or SNN. It is necessary to tease out visceral from somatic pain prior to the block, and sometimes it may be necessary to do a diagnostic block with local anesthetic. Appropriate assessment and optimal patient selection will define the outcome of the block. Patients with uncorrectable coagulopathy and active infection are not ideal candidates. CPN and SPN can cause unopposed parasympathetic activity and increase bowel motility and should be avoided when there is a concern for bowel obstruction. Review of the scans for involvement of the celiac plexus and extent of disease is necessary prior to the needle placement. There is a decreased efficacy of the block with nodal involvement and disease around the celiac plexus (27).

Neurolysis Technique

There are multiple techniques to access blockade of the celiac plexus and the splanchnic nerves. This can be achieved using fluoroscopy, ultrasound, endoscopic, or CT guidance. A fluoroscopically guided retrocrural approach to the splanchnic nerves is the commonly adopted technique in our practice.

Transcrural celiac plexus block

Fluoroscopically guided transcrural celiac plexus block is performed by pain physicians in an office or the operating room setting as dictated by the medical condition of the patient. The patient is kept Nil per os and hydrated with 500 – 1000 mL of fluids pre procedure. Routine monitors are applied and the patient is laid prone on the procedure table. After sterile preparation and draping, the vertebral bodies are identified using the fluoroscopy. The c-arm is obliqued 20 to 30 degrees until the tip of the transverse process at the L1 vertebral body overlies the anterolateral margin (Fig. 4). The skin and subcutaneous tissues are anesthetized with local anesthetic. A 22 gauge 5 – 7 inch spinal needle can be used based on the patient body habitus. A transaortic

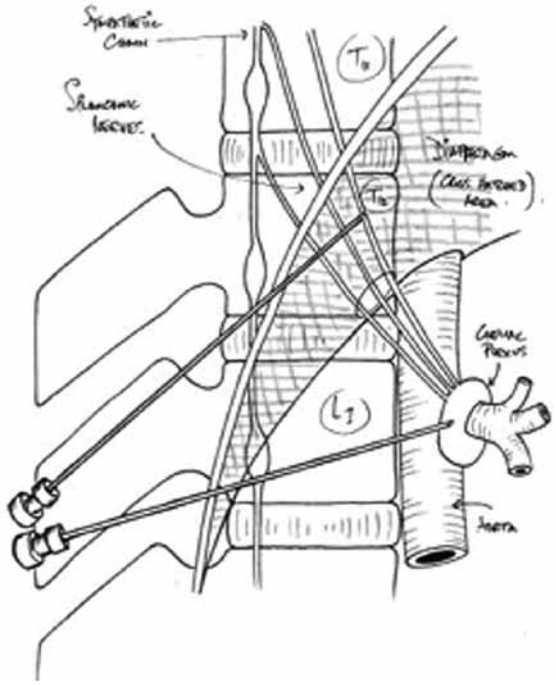

Fig. 4. *Schematic description of the retrocrural splanchnic nerve neurolysis (SNN) versus the transcrural celiac plexus neurolysis (CPN). The target for the retrocrural SNN is the anterolateral border of the T12 vertebral body. This position is posterior to the crus of the diaphragm, leading to destruction of the splanchnic nerves before they penetrate the crus. The target for the transcrural CPN anterior to the abdominal aorta at the L1 vertebral level. This needle position leads to the destruction of the celiac plexus itself. Image courtesy of Dr. S. G. Tordoff.*

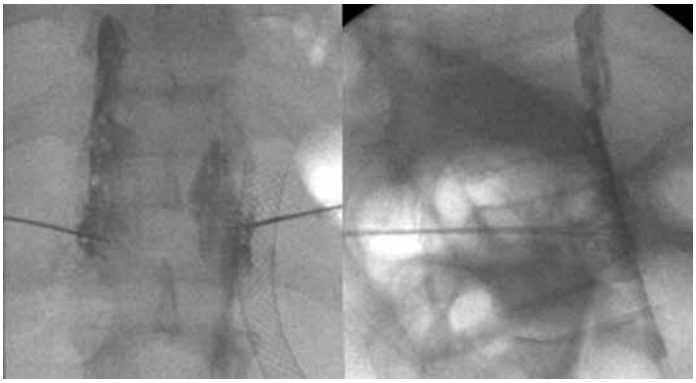

Fig. 5. *Anteroposterior and lateral fluoroscopic images showing final needle position for the splanchnic nerve neurolysis. The figure demonstrates a bilateral technique with appropriate anterolateral contrast spread.*

technique can be performed using a single needle from the left side. The needle is advanced towards the anterolateral margin of the vertebral body with frequent images in the anteroposterior and lateral views. Once the needle is positioned at the anterolateral margin of the L1 vertebral body, it is advanced 2 – 3 cm anterior with fluoroscopic aid as well as continuous aspiration. Once blood is aspirated, the needle is advanced to traverse anterior to the aorta until one can no longer aspirate blood. Needle position is confirmed by injecting dye to see contrast spread anterior to the aorta. If there is not adequate spread across the midline to the right, a second needle on the opposite side should be placed. Diagnostic block with 10 mL of 2% chlorprocaine is performed and a total of 20 mL of neurolytic agent is injected incrementally.

Retrocrural technique (splanchnic block)

Figs. 4 and 5 show a modification of the transcrural technique performed at the level of T11 or T12. The pre-procedure preparation and positioning are similar. The fluoroscopy beam is obliqued 20 to 30 degrees until the transverse process of T12 is flush with vertebral body. A 22 gauge 5 – 7 cm spinal needle is used for the procedure. The needle is advanced to the anterolateral margin of the vertebral body with frequent images. Once the needle is at the anterolateral margin, it is advanced to the anterior border of the vertebral body in the lateral view. A similar needle placement is done on the opposite side. After negative aspiration, dye is injected to confirm spread over the anterior vertebral body and ensure no posterior tracking. Five mL of 2% chlorprocaine is injected for diagnostic purposes followed by 10 mL of the neurolytic agent through each needle incrementally. Two mL of local anesthetic is injected to flush the neurolytic agent; the stylette is placed and needle removed.

The present study primarily utilized the retrocrural SNN technique. The traditional transcrural technique is performed at the L1 vertebral body level with final needle position anterior to the abdominal aorta near the celiac artery (superior needle in Fig. 4). The retrocrural approach for this study was generally performed bilaterally at the T12 vertebral body level with final needle position along the anterolateral border of the vertebral body (inferior needle in Fig. 4; Fig. 5). Following initial needle placement, 2% chlorprocaine was

injected through each needle. After appropriate hip flexion, strength was documented 15 minutes later and either phenol or alcohol was slowly injected through each needle.

Complications

Complications related to CPN and SNN differ with the technique used. Ischia et al (28) compared the complications and efficacy of the block using the classic retrocrural, bilateral splanchnic, and transaortic techniques. The incidence of hypotension was more frequent with the retrocrural (50%) and splanchnic (52%) techniques possibly from sympathetic chain neurolysis. The incidence of increased defecation was more frequently seen after an anterocrural transaortic approach (65%). The incidence of transient complications of hematuria, hiccoughing, interscapular back pain, reactive pleurisy, and dysestheisa were similar in all 3 groups. There are reports of gastroperesis and gastric perforation as well as retroperitoneal fibrosis (29).

The most common complication related to the sympathectomy is increased defecation and hypotension. These are usually transient, and to some extent, hypotension can be prevented by adequate hydration and intravenous fluids pre procedure. On occasions these can be prolonged requiring hospitalization and treatment with intravenous hydration. Orthostatic hypotension can be prolonged and last for up to 5 days (30). Treatment includes adequate hydration, bed rest with legs raised and wrapped in elastic stockings, and avoidance of sudden changes in position. Increased defecation can lead to severe dehydration in debilitated patients. Treatment includes aggressive hydration (oral or parenteral) and antidiarrheal agents.

Renal injury and hematuria, intravascular injection, and pneumothorax are complications related to needle positioning. Use of CT or ultrasound guidance for the block will allow visualization of the kidney and pleura with a decreased incidence of these complications. Transaortic approaches can lead to rupture or aortic dissection and hemorrhage. This technique should be avoided in patients with aortic atherosclerotic disease. Retroperitoneal hemorrhage is a rare complication and should be suspected when the patient complains of backache and hypotension after the block. Backache is frequently seen from the needle trauma as alcohol irritation of the retroperitoneal structures. Serial hematocrits should be performed for persistent backache to rule out retroperitoneal bleed and radiologic imaging as indicated.

Alcohol is painful on injection and it is necessary to inject prior local anesthetic or provide sedation. Accidental intravascular injection of 30 mL of 100% ethanol can lead to blood alcohol levels above the legal driving limit. Inadvertent intravascular injection of phenol can lead to manifestations similar to local anesthetic toxicity and can lead to seizures and cardiovascular collapse (21). Tracking of the neurolytic agent to the neuraxis or nerves can lead to neuritis.

Although infrequent, one of the most devastating complications related to a neurolytic celiac plexus block is paraplegia. The incidence of this complication appears to be less than 1:1000. It is theorized that the cause of paraplegia is due to spread of the neurolytic agent to the posterior surface of the aorta at the spinal segmental arteries. This can lead to spasm of the segmental arteries that perfuse the spinal cord. The neurolytic agent can also cause necrosis or occlusion of the Artery of Adamkiewicz leading to paraplegia. No major complications were noted in the current study.

Efficacy

Overall, there is significant evidence from controlled trials that the celiac plexus block is effective for pancreatic cancer related pain. There are numerous techniques adopted to perform the block with the use of fluoroscopy, ultrasound, and endoscopic and CT guidance. There is limited evidence comparing the various techniques to look at efficacy and side effects. The authors of a 2011 Cochrane review of CPN for pancreatic cancer pain concluded that "although statistical evidence is minimal for the superiority of pain relief over analgesic therapy, the fact that celiac plexus block causes fewer adverse effects than opioids is important for patients" (31). Six studies with 358 patients met inclusion criteria (severe pain in patients with unresectable pancreatic cancer) (1,32-36). Endoscopic-guided CPN provides detailed imaging of the blood vessels around the plexus and theoretically is superior to the fluoroscopically guided posterior percutaneous approach, though there is a lack of comparative studies to demonstrate this. Yan and Myers (37) did a systematic review (1966 through 2005) to examine the efficacy and safety of CPN in randomized controlled trials. There were 302 patients in the 5 studies that met criteria (1,32-34,38). CPN was associated with better pain control, decreased opioid requirement, and improved constipation. Survival rates were not different and it was difficult to assess change in quality of life (QOL) due to different outcome scales with each study.

Ischia et al (28) showed that patients with pancreatic cancer benefit from CPN done early in the course of the disease when the pain is of "celiac type." Seventy to eighty percent of the patients had pain relief immediately after the block that was sustained in 60 to 75% until death. CPN by itself was not adequate to for complete pain relief, but showed substantial benefit by abolishing the visceral pain component. In a study by De Cicco et al (27) analgesic benefit based on the injectate spread was assessed. Pain relief with a CT guided anterior approach was dependent upon appropriate spread in the 4 quadrants around the celiac artery which was hampered by regional anatomic variations. One hundred percent of the patients had "long lasting" pain relief with spread in all 4 quadrants and dropped to 48% with spread in 3 quadrants. None of the patients with injectate spread in one or 2 quadrants had any long-lasting pain relief. They concluded that long-lasting analgesia was obtained with a complete, 4 quadrant spread of the neurolytic agent. Anatomic distortions from local cancer and or previous therapies hampered spread of the agent and showed lower efficacy of the block.

In this retrospective study, a total of 93 patients underwent SNN for cancer related pain during the study period. This approach (retrocrural splanchnic) was taken due to a lower risk of aortic puncture, the ability to use smaller volumes of neurolytic injectate, and because efficacy of this approach is less likely to be compromised by anatomic differences due to tumor burden or adenopathy within the upper GI system (39).

The major finding of this study was that one month post-procedure pain scores were not different between those treated with alcohol (4.23 ± 2.69, 4 [1, 9]) versus phenol (3.87 ± 2.53, 4 [0, 10]; $P = 0.658$). In addition, no difference in complications was seen between the agents either. As such, either of these agents appears to be both appropriate and equivalent to utilize for the SNN technique. Choice of neurolytic medication can appropriately be left to the clinical judgment and local availability of the treating physician.

Comparing pre- and one month post-procedure, SNN produced pain reduction averaged 1.17 ± 2.77 (-1 [-10, 5]) on an 11 point numeric pain scale. Importantly, no reduction in morphine equivalent dose utilization was detected after neurolysis. Interestingly, the procedure produced significant improvements in anxiety, depression, difficulty thinking clearly, and feeling of well-being. To further explore the pain reduction observed, we categorized the patients to responders and non-responders based on their pain score reduction using different thresholds (Fig. 3). The responder analysis demonstrated that greater than or equal to 30%, 50%, and 70% pain reduction was present in 44.57%, 31.52%, and 17.39% of the patients, respectively. Interestingly, 43.54% of the patients had either unchanged or worsened pain after the procedure. As such, among patients with ≥ 30% pain reduction, the actual pain relieving effect was much greater than 1.2 (the average pain change for these patients [n = 41] was -3.57 ± 1.81,-3 [-10,-1]) because the overall effect was diluted by the 43.5% of patients that did not achieve pain relief. The difference in the rate of response (for using each of the 3 thresholds) was not significant between alcohol and phenol. Patients who had alcohol are more likely to have 0 – 30% ($P = 0.001$), 0 – 50% ($P = 0.003$), and 0 – 70% ($P = 0.004$) feeling of well-being score reduction, 0 – 50% fatigue score reduction ($P = 0.043$) than patients who had phenol. Possible etiologies for failure to produce pain relief include technically unsuccessful blocks due to anatomical or technical considerations, multiple sources of significant pain, and frank disease progression.

Other disease state and treatment effects previously suggested to be important in the efficacy of CPN and SNN were not found to be important in this study. Specifically, the presence of celiac axis tumor or nodal involvement and prior radiation therapy did not impact the reduction in numeric pain score, ESAS items, or morphine equivalence utilization. The authors attribute this to the predominant use of SNN and therefore avoiding the anatomic distortions associated with celiac disease or previous treatment.

The procedure also significantly reduced depression, anxiety, and difficulty thinking clearly at one month. In addition, feeling of well-being trended towards improvement.

GI cancer teams have recommended palliative care at the initiation of treatment for patients with poor relative survival rates and an intractable symptom burden profile. For these patients, the goal is often promoting quality of life (18). In our study, we demonstrated positive outcomes in biological and psychological factors among such patients. Our study, like others supporting the biopsychosocial model of pain (40), demonstrates the interplay of various factors in the cancer pain experience. Unlike recent research which established an evidence base for certain psychosocial interventions for cancer pain (41), our study approached treatment with a medical intervention for a specific patient population.

Our interventional approach to treatment demonstrated similar results to those psychological interventions (41). A limitation of our study is that we did not fully assess the biopsychosocial symptom burden. A recommendation for future studies is that a broader range of symptoms be assessed, including social support and interpersonal connections. By so doing, it would be possible to assess the extent to which improvement in pain and mood is also associated with improved psychosocial experiences as well.

Conclusion

This study presents a retrospective chart review of 93 patients who underwent splanchnic nerve neurolysis for cancer related upper abdominal pain in order to describe patient characteristics, examine comparative efficacy, duration of benefit, and incidence of complications with alcohol vs. those of phenol. Approximately half of cases studied related to pancreatic cancer, whereas gastric cancer or abdominal metastases accounted for nearly equal portions of the rest of patients included. Consistent with previous studies, SNN reduced reported pain scores while not significantly reducing opioid consumption. No difference in pain outcomes was found comparing alcohol versus phenol based neurolytic techniques. Celiac axis tumor infiltration and pre-procedural local radiation therapy did not change the effectiveness of the procedure. The authors attribute this to the use of SNN as opposed to CNN. Interestingly, the procedure produced significant improvements in anxiety, depression, difficulty thinking clearly, and feeling of well-being. The change in ancillary symptoms has a theoretical basis that supports a biopsychosocial model of pain since changes in one target area (pain) impact other related ones (depression and anxiety). No major complications were reported. SNN showed to be an effective and relatively safe procedures for the treatment of pain associated with pancreatic and other upper abdominal organ malignancies in our sample of patients. The authors recognize the retrospective nature and the small sample of patients in this study.

Acknowledgments

Dr Simon Tordoff, FRCA FFPMRCA, Consultant in Anaesthesia and Pain Medicine for giving copyrights to Fig. 4.

Dr Dinesh Keerty for help with data collection.

Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

References

1. Wong GY, Schroeder DR, Carns PE, Wilson JL, Martin DP, Kinney MO, Mantilla CB, Warner DO. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: A randomized controlled trial. *JAMA* 2004; 291:1092-1099.
2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. *Ann Oncol* 2007; 18:1437-1449.
3. *Cancer Facts & Figures 2013*. American Cancer Society, Atlanta, 2013.
4. Nagels W, Pease N, Bekkering G, Cools F, Dobbels P. Celiac plexus neurolysis for abdominal cancer pain: A systematic review. *Pain Med* 2013; 14:1140-1163.
5. Keefe FJ, Abernethy AP, L CC. Psychological approaches to understanding and treating disease-related pain. *Annual Review of Psychology* 2005; 56:601-630.
6. Zaza C, Baine N. Cancer pain and psychosocial factors: A critical review of the literature. *J Pain Symptom Manage* 2002; 24:526-542.
7. Kroenke K, Krebs E, Wu J, Bair MJ, Damush T, Chumbler N, York T, Weitlauf S, McCalley S, Evans E, Barnd J, Yu Z. Stepped Care to Optimize Pain care Effectiveness (SCOPE) trial study design and sample characteristics. *Contemporary Clinical Trials* 2013; 34:270-281.
8. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: Examining quality of life in diverse cancer survivors. *Cancer* 2011; 117:1994-2003.
9. Wilkie DJ, Keefe FJ. Coping strategies of patients with lung cancer-related pain. *Clin J Pain* 1991; 7:292-299.
10. Turk DC, Monarch ES, Williams AD. Cancer patients in pain: Considerations for assessing the whole person. *Hematology/Oncology Clinics of North America* 2002; 16:511-525.
11. Otis-Green S, Sherman R, Perez M, Baird RP. An integrated psychosocial-spiritual model for cancer pain management. *Cancer Practice* 2002; 10:S58-S65.
12. Spiegel D, Sands S, Koopman C. Pain and depression in patients with cancer. *Cancer* 1994; 74:2570-2578.
13. PJacobsen PB, Donovan KA, Swaine ZN, Watson IS. Management of anxiety and depression in adult cancer patients: Towards an evidence-based approach. In: *Oncology: Evidence-Based Approach*. Springer, New York, 2006, pp 1552-1579.
14. Newport DJ, Nemeroff CB. Assessment and treatment of depression in the cancer patient. *Journal of Psychosomatic Research* 1998; 45:215-237.
15. Stark DP, House A. Anxiety in cancer patients. *Br J Cancer* 2000; 83:1261-1267.

16. Von Korff M, Simon G. The relationship between pain and depression. *Br J Psychiatry Suppl* 1996; 30:101-108.
17. Novy DM, Aigner CJ. The biopsychosocial model in cancer pain. *Curr Opin Support Palliat Care* 2014; 8:117-123.
18. Lazenby JM, Saif MW. Palliative care from the beginning of treatment for advanced pancreatic cancer. Highlights from the 2010 ASCO Gastrointestinal Cancers Symposium. Orlando, FL, USA. January 22-24, 2010. *JOP* 2010; 11:154-157.
19. Raj PP. Visceral pain. *Agri* 2004; 16:7-20.
20. Burton AW, Phan PC, Cousins MJ. Treatment of cancer pain: Role of neural blockade and neuromodulation. In: *Neural Blockade in Clinical Anesthesia and Pain Medicine.* Lippincott Williams and Wilkins, Philadelphia, 2009, pp 1111-1153.
21. Molloy R, Benzon H. Neurolytic blocking agents: Uses and complications. In: *Raj's Practical Management of Pain.* Mosby Elsevier, Philadelphia, PA, 2008, pp 839-850.
22. Rumsby MG, Finean JB. The action of organic solvents on the myelin sheath of peripheral nerve tissue. II. Short-chain aliphatic alcohols. *J Neurochem* 1966; 13:1509-1511.
23. Smith MC. Histological findings following intrathecal injections of phenol solution for relief of pain. *Br J Anaesth* 1964; 36:387-406.
24. Kocabas H, Salli A, Demir AH, Ozerbil OM. Comparison of phenol and alcohol neurolysis of tibial nerve motor branches to the gastrocnemius muscle for treatment of spastic foot after stroke: A randomized controlled pilot study. *Eur J Phys Rehabil Med* 2010; 46:5-10.
25. Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; 23:129-138.
26. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000; 88:2164-2171.
27. De Cicco M, Matovic M, Bortolussi R, Coran F, Fantin D, Fabiani F, Caserta M, Santantonio C, Fracasso A. Celiac plexus block: Injectate spread and pain relief in patients with regional anatomic distortions. *Anesthesiology* 2001; 94:561-565.
28. Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. *Anesthesiology* 1992; 76:534-540.
29. Moore JC, Adler DG. Celiac plexus neurolysis for pain relief in pancreatic cancer. *J Support Oncol* 2009; 7:83-87, 90.
30. Leon-Casasola Od. Neurolysis of the sympathetic axis for cancer pain management. In: *Raj's Practical Managament of Pain.* Mosby Elsevier, Philadelphia, PA, 2008, pp 917-925.
31. Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. *The Cochrane Database of Systematic Reviews* 2011; 16:CD007519.
32. Lillemoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993; 217:447-455; discussion 456-447.
33. Kawamata M, Ishitani K, Ishikawa K, Sasaki H, Ota K, Omote K, Namiki A. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain* 1996; 64:597-602.
34. Mercadante S. Celiac plexus block versus analgesics in pancreatic cancer pain. *Pain* 1993; 52:187-192.
35. Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia S. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *The British Journal of Surgery* 1998; 85:199-201.
36. Zhang CL, Zhang TJ, Guo YN, Yang LQ, He MW, Shi JZ, Ni JX. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. *Dig Dis Sci* 2008; 53:856-860.
37. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. *Am J Gastroenterol* 2007; 102:430-438.
38. Polati E, Luzzani A, Schweiger V, Finco G, Ischia S. The role of neurolytic celiac plexus block in the treatment of pancreatic cancer pain. *Transplant Proc* 2008; 40:1200-1204.
39. Rathmell J. *Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine.* Wolters Kluwer/Lippincott Williams & Williams, Philadelphia, 2012.
40. Syrjala KL, Chapko ME. Evidence for a biopsychosocial model of cancer treatment-related pain. *Pain* 1995; 61:69-79.
41. Sheinfeld Gorin S, Krebs P, Badr H, Janke EA, Jim HS, Spring B, Mohr DC, Berendsen MA, Jacobsen PB. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. *J Clin Oncol* 2012; 30:539-547.