Randomized Controlled Trial

Comparison Between Two Volumes of 70% Alcohol in Single Injection Ultrasound-Guided Celiac Plexus Neurolysis: A Randomized Controlled Trial

Mohamed E. Abdel-Ghaffar, MD, Salah A. Ismail, MD, Reda A.Ismail, MD, Mostafa M. Abdelrahman, MD, and Mohamed E. Abuelnaga, MD

From: Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Suez Canal University

Address Correspondence: Mohamed E. Abuelnaga, MD, Suez Canal University P.O. Box 41522 Ard Elgameiat, Ismailia city, Egypt. E-mail: Mohamed_abuelnga@med.suez.edu.eg

Disclaimer: There was no external funding in the preparation of this manuscript.

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.

Manuscript received: 08-02-2021
Revised manuscript received: 11-22-2021
Accepted for publication: 01-13-2022

Free full manuscript: www.painphysicianjournal.com

Background: Pain due to inoperable upper abdominal malignancies is a challenging condition that needs a multimodal analgesic regimen to be managed properly. Celiac plexus alcohol neurolysis was proved to be effective in relieving such type of pain; however, there is no consistent data about the optimal volume to be used to maintain the balance between the neurolytic effect and the destructive effect of alcohol.

Objectives: We aim to compare the analgesic effect of 2 different volumes of alcohol to improve the outcome of interventional management.

Study Design: This was a randomized controlled double-blinded interventional clinical trial.

Setting: Single university hospital.

Methods: Thirty-two patients who suffered from abdominal pain due to unresectable abdominal malignancies were randomly allocated to receive in a single injection ultrasound-guided celiac plexus neurolysis (CPN) with injection of either 20 mL 70% alcohol (CPN20 group) or 40 mL 70% alcohol (CPN40 group). The primary outcome was the post-procedure pain score, while the secondary outcomes included the post-procedure total daily opioid consumption and quality of life (QOL).

Results: There was no statistically significant difference between both groups regarding visual analog scale (VAS) scores at all time points (P-value > 0.05); however, comparisons in each group revealed significantly reduced VAS scores at all time points following the intervention when compared to the baseline. Daily morphine equivalent consumption doses showed statistically significant differences between the baseline and each time point in both groups (P value < 0.05), with no significant difference between both groups at each time point (P value > 0.05). There was no statistically significant difference between the study groups regarding all domains in quality of life assessment at all time points (P value > 0.05). The scores of most time points in all domains were different significantly when compared to the baseline readings in both groups, with a tendency to decline over time in both groups approaching the baseline values.

Limitations: This was a single-center study with a relatively small sample size. Further prospective, multicenter, randomized, and controlled studies with a larger sample size are required to confirm the effects in this study.

Conclusions: During ultrasound-guided CPN for patients with inoperable upper abdominal cancers who failed medical management, a volume of 20 mL is as effective as 40 mL of 70% alcohol regarding pain control, opioid consumption, quality of life, and procedure-related complications.

Kew words: Upper abdominal pain, upper abdominal malignancy, ultrasound-guided celiac plexus block, RCT, celiac plexus neurolysis, alcohol neurolysis, opioid consumption, quality of life

Pain Physician 2022: 25:293-303

Management of pain due to abdominal malignancies is a challenging clinical scenario that involves multiple steps with variable results. Patients with inoperable upper abdominal malignancies can be managed with medical treatment for their pain, but sometimes it becomes ineffective, or its side effects limit its use. In these cases, interventional methods like celiac plexus neurolysis (CPN) can help to improve the response to the medical treatment or even reduce the daily doses required and hence reduce the side effects (1).

The aim of all pain management approaches in these patients is to improve the quality of their lives, considering the aggressive nature of these cancers and the high mortality rates (2).

The celiac plexus (CP) is a part of the autonomic nervous system that transmits pain from most of the upper abdominal organs including the liver, pancreas, spleen, stomach, kidney, aorta, mesentery, and small bowel (3).

Multiple approaches to block the CP have emerged since the first description by Kappis in 1914. Posterior approaches included the classic retrocrural, the anterocrural, the transaortic, and the transdiscal approaches (3). These posterior approaches used the insertion of 2 needles, one on either side at the level of the first lumbar vertebra with fluoroscopic guidance (4). They are associated with many complications, including paraplegia and serious neurological complications due to injury of Adamkiewicz's arteries or the small nutrient vessels supplying the spinal cord, or even injury of the nervous tissues in the pass of the needle (3).

Computed tomography and ultrasound provided the ability to perform the celiac plexus block (CPB) through the anterior abdominal wall with results equivalent to or better than posterior approaches (5).

Ultrasound-guided anterior approach gives the operator and the patient many advantages. It includes the ability to completely monitor the entire procedure in real time, avoidance of inadvertent major vessel injury (6), and the ability to identify the true location of the CP even if it was displaced due to the mass effect of the tumor (7). Moreover, the use of the supine position is much more comfortable for the patient. In addition, ultrasound guidance is less expensive and carries fewer neurological and radiation risks (8). No significant needle-related complications were reported during ultrasoundguided anterior approach CPN, despite the fact that the needle can pass through the liver, the pancreas, or the stomach (6). Moreover, the use of blunt block needles was associated with less vascular injuries. In the study done by Akin et al (9), 1989, they failed to cause renal artery injury in 4 dogs after more than 100 direct intended attempts using blunt needles.

The use of alcohol for neurolysis is evidenced by many studies; however, the data regarding the volume of alcohol injected is not consistent (10). The destructive effect of the alcohol is not limited to the CP nervous tissue alone, but rather it affects all the soft tissues encountered by the injected volume (11). Balancing between the neurolytic effect and the destructive effect is the rule of the volume of alcohol used.

Dolly A et al (12) reported that the duration of using 20 mL of alcohol was only half of that obtained using 40 mL of alcohol. The small calculated sample size of this study (5 patients in each group) and the unoptimized medical management after the block raised the question of the ability to generalize these results. For this reason, this study was designed to try to identify the difference between 2 volumes of alcohol in ultrasound-guided anterior approach CPN for patients with inoperable upper abdominal cancers, aiming to improve the outcome of interventional pain management in these patients. The primary objective was to compare the pain relief effect of ultrasound-guided percutaneous CPN using 20 mL versus 40 mL of 70% alcohol regarding visual analog scale (VAS) scores. While the secondary outcomes were the total daily opioid consumption and the quality of life (QOL) in both groups using the 4 domains of the general functional assessment of cancer therapy scale (FACT-G) (13).

Methods

This study is a prospective randomized controlled double-blinded clinical interventional trial. After obtaining approval from the Faculty Ethics Committee, this study was conducted on 32 patients who suffered from abdominal pain due to unresectable abdominal malignancies. Patients and outcome assessors were blinded to the study groups. This manuscript adheres to the applicable Equator guidelines (www.consort-statement.org). This trial was registered at the PACTR (www.pactr.org) database before enrolment of the first patient (PACTR201803003212106, Date of registration: 22 March 2018). Written informed patient consent was obtained from each patient enrolled in this study.

Inclusion criteria included adult patients of either gender, 18 years or older, patients with the diagnosis of histologically proven or radiologically consistent, surgically unresectable upper abdominal malignancies, patients with VAS scores of equal to or more than 4/10 due to can-

cer-related visceral pain despite adequate conventional medical management (defined as the highest analgesia possible without intolerable side effects using opioid and non-opioid drugs according to the world health organization analgesic step ladder) or who suffered from side effects limiting the use of these drugs.

Exclusion criteria included patients who received celiac or splanchnic blocks previously as neurolytic management for cancer pain, patients who received intrathecal or epidural interventional implantable devices for cancer pain, allergy to local anesthetics used in the diagnostic block, coagulopathies not correctable with active medical management, patients with an abdominal vascular aneurysm or aortic grafts or stents, patients with uncontrolled hypotension, patients suffering from severe pain not related to the abdominal malignancy, patients with documented metastatic lesions in other sites of the body contributing to pain severity, patients with psychiatric disorders preventing adequate assessment and data collection, inadequate identification of the celiac trunk and other anatomical landmarks during the preliminary ultrasound scanning, failed response to the local anesthetic CP test block or patients refusing to participate in the study.

Patients were randomly allocated to one of the 2 equal study groups by an assistant anesthesiologist using a computer-generated simple random table (http://www.randomizer.org), and randomization sequence was concealed in opaque sealed numbered envelopes which were opened on the day of the procedure by a head nurse who was neither involved in patient's preparation nor data collection following a successful local anesthetic test block. Group I (CPN 20): (16 patients) received 20 mL 70% alcohol in a single injection ultrasound-guided CPN, while in Group II (CPN 40): (16 patients) received 40 mL 70% alcohol in a single injection ultrasound-guided CPN.

Pre-Procedure Preparation:

All enrolled patients had a thorough familiarization session with the VAS scores and FACT-G questionnaire.

A full assessment of the medical condition and pain severity, including history, physical examination, and laboratory and radiological assessment, was obtained from all patients. Medical history included chronic medical disorders, past anesthetic history, the duration of pain, episodes of breakthrough pain, current analgesic medications, and history of interventional management for the pain condition. Physical examination included general examination, vital signs, heart, chest, and abdominal examinations, and examination for exclusion of other sources for pain. Investigations included complete blood count, coagulation profile, with the review of the patient's computed tomography and magnetic resonance images if present to assess the mass effect and the relations of the abdominal aorta, as well as planning the possible needle access. Patients were fasting for 4 to 6 hours; an 18-gauge venous cannula was inserted into a large vein, and an infusion of 1000 mL of lactated Ringer was started. Heart rate, oxygen saturation, and blood pressure were monitored as baseline values then every 3 minutes. Patients were positioned in the supine position, and general abdominal ultrasound scanning was done before injection to assess the anatomical relations of the aorta and to assess for the ability to perform the block technique. At this point, patients with obscured ultrasound views were excluded and shifted to a standard posterior approach using fluoroscopic guidance. Patients with adequate ultrasound views were prepared for ultrasound guidance, and complete sterilization and draping of the abdomen and full surgical scrubbing of the operator were ensured.

Procedure Description:

Using the Sonosite M-Turbo® ultrasound machine, the curved array probe (2-5MHz) was positioned in the cross-sectional plain just below the xiphoid process, and identification of the abdominal aorta was done by tilting the probe slightly cephalic. Then caudal sliding was done to identify the celiac trunk branching from the anterior wall of the aorta and characterized by its bifurcation into right (hepatic) and left (splenic) branches, and then the probe was moved slightly caudate to identify the superior mesenteric artery. From this point, the probe was rotated 90° to obtain the long axis view of the aorta and these 2 branches. The entry point was identified according to accessibility and presence of a clear non-vascular pathway (either midline in the long axis or the short axis through a trans-hepatic or a trans-gastric approach). After infiltration of the skin and subcutaneous tissues with 3 mL lidocaine 1%, a 20-gauge 20 cm length CHIBA needle was introduced under direct vision with in-plane technique to reach the point between celiac and superior mesenteric arteries above the aortic wall. A diagnostic block was done by injecting 20 mL bupivacaine 0.25% through the needle, and assessment of pain relief within the following 20 minutes to assess responsiveness to the block. If the patient demonstrated improvement in pain intensity, defined as a reduction ≥ 50% compared to baseline, then

the patient was considered responsive, and his envelop was opened by the head nurse to find out his group allocation to receive alcohol neurolysis. The alcohol injectate was prepared by the head accordingly. This nurse will take no further role in the study. Otherwise, the patient was excluded from the study and was reassessed after 48 hours for possible benefit from neurolysis if a delayed response was documented. Patients in the first group (CPN20) received 20 mL of 70% alcohol, while patients in the second group (CPN40) received 40 mL of 70% alcohol. The CHIBA needle was then flushed using 2 mL of normal saline before removing it to avoid injury to the tissues with the remaining alcohol in the needle (Fig. 1).

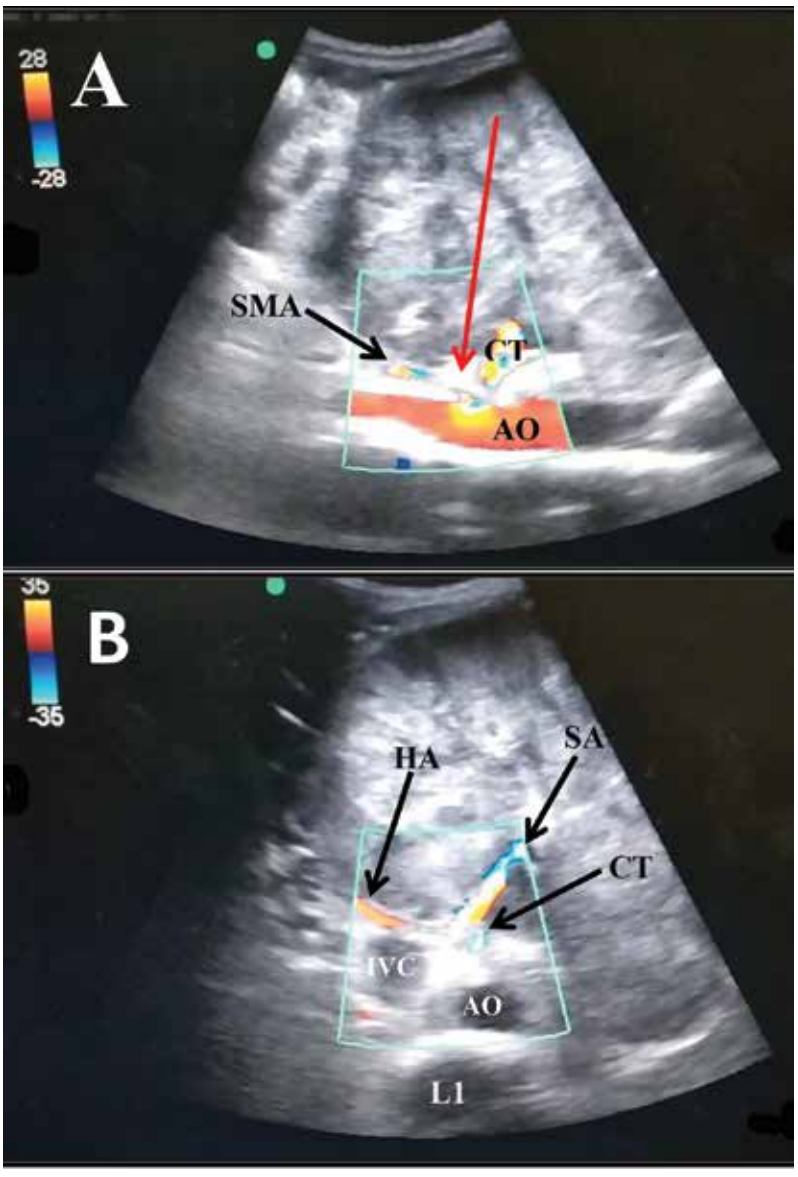

Fig. 1. A: *Longitudinal ultrasound view of the aorta (AO), the celiac trunk (CT), and the superior mesenteric artery (SMA). The red arrow represents the Needle path between the two branches*, B: *Cross-sectional ultrasound view of the aorta (AO), celiac trunk (CT), hepatic artery (HA), splenic artery (SA), inferior vena cava (IVC), and first lumbar vertebral body (L1).*

Post-procedure: If the patient's blood pressure was ever reduced to less than 20% of the baseline, infusion of intravenous normal saline was started until normalization of the blood pressure. Ephedrine 9 mg intravenously was given as needed. A course of ciprofloxacin 500 mg twice daily for 5 days was commenced in all patients as prophylaxis. Patients were observed over the next 24 hours in the oncology ward and then discharged if the hospital stay was uneventful. Assessment of VAS scores was done one hour, 24 hours after the block, then every week for 12 successive weeks. FACT-G QOL questionnaire was obtained by interviewing the patient at one week, 4 weeks, 8 weeks, and 12 weeks after the procedure. If pain decreased after the intervention, the opioid dose was reduced to half, and then continued dose reduction by 50% daily was done until pain occurred, or the patient was taking 60 mg modified-release morphine per day. At this point, opioids were stopped or replaced by regular weak opioids according to clinical judgment. Adjuvant analgesia was also described for patients if pain could not be relieved by opioids. The total daily opioid requirements equivalent to mg/day of oral morphine at each time point were recorded. Complications of the procedure were reported, including hypotension, diarrhea, hematoma, infection, neurologic complications, and mortality.

Statistical Analysis

SPSS Version 22.0 (IBM Corp,

Armonk, NY) for Windows operating system was used for performing the statistical analysis. Descriptive data were expressed as mean and SD for continuous variables, or count/total and percentages (%) for categorical and dichotomous variables except where otherwise indicated. The normality of data was verified using the Kolmogorov-Smirnov test and visual inspection of histograms. The categorical and dichotomous variables between the 2 studied groups were analyzed using The chi-square test, while Student t-test and Mann-Whitney U test were used to analyze the parametric and the non-parametric continuous variables between the 2 studied groups, respectively. Paired sample t-test and Sign test were used to analyze the parametric and the non-parametric continuous variables among the follow-up points within the same group, respectively. The level of statistical significance was considered to be $P < 0.05$. A sample size of 14 patients per group was required to detect 1.64 difference between the means of VAS scores at 12 weeks following CPB with the volume of 40 mL and means of VAS scores at 12 weeks following CPB with the volume of 20 mL at a standard deviation of 1.3 (14,15) with 90% power and a 5% level of significance. After considering a drop out of 10%, the required sample size was 32 patients (16 patients per group).

Results

Thirty-two patients were randomly allocated to 2 equal groups, CPN20 and CPN40 groups (Fig. 2).

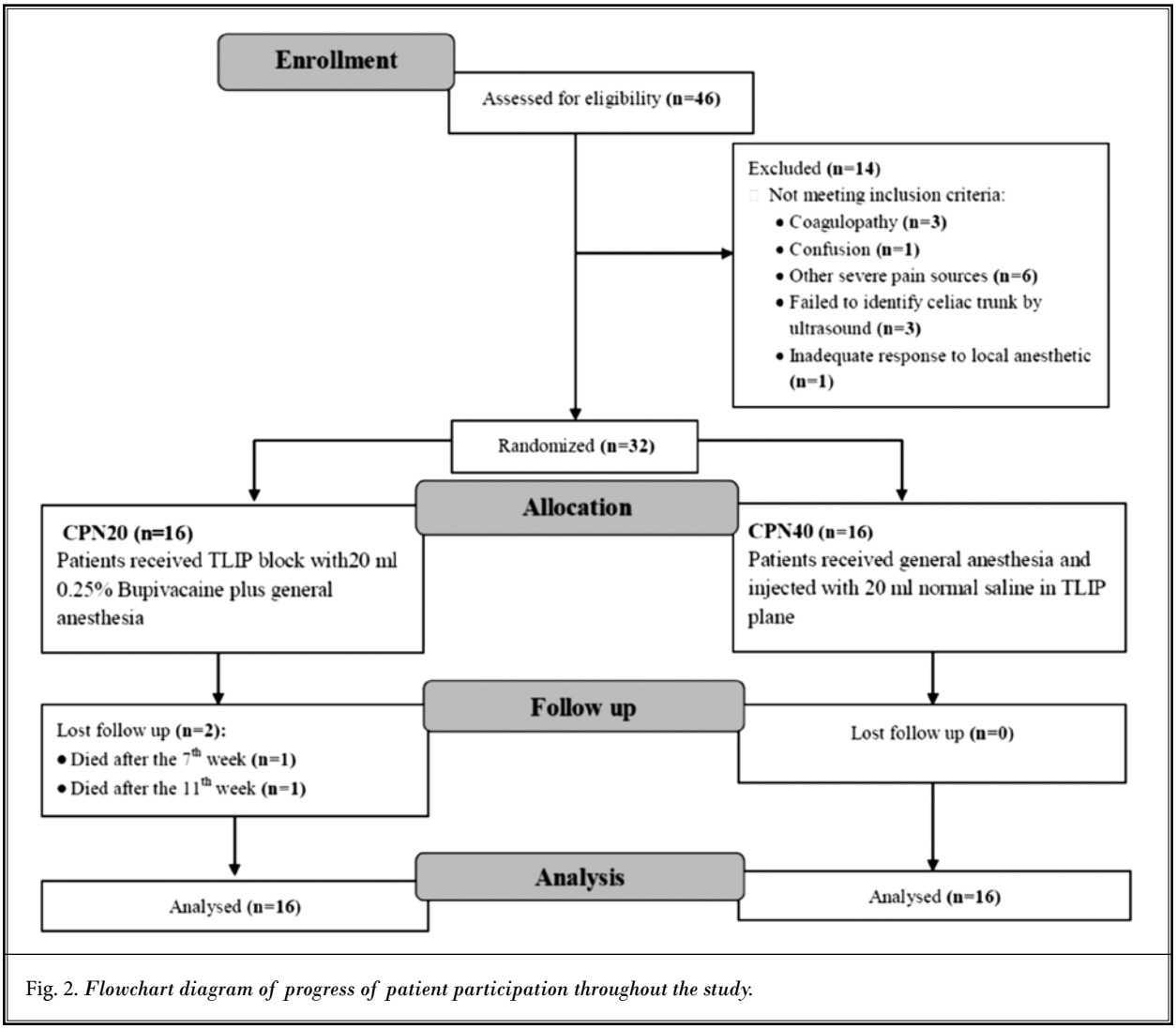

Fig. 2. *Flowchart diagram of progress of patient participation throughout the study.*

Both groups were matched regarding basic characteristics, including age and gender. There was no statistically significant difference between the 2 groups regarding the presence of chronic illnesses, cancer characteristics including cancer type, confirmation method, metastatic lesions, primary cancer management received, and sites of pain (Table 1).

No statistically significant difference was found between both groups regarding VAS scores at all time points (*P* value > 0.05), with mean values less than 3 cm at all points after the intervention. Comparisons in each group revealed significantly reduced VAS scores at all time points following the intervention when compared to the baseline (Fig. 3).

Daily morphine equivalent consumption doses in milligrams showed statistically significant differences between the baseline and each time point in both groups (*P* value < 0.05), with no significant difference between both groups at each time point (*P* value > 0.05). However, within each group, compared to the baseline value, the 4th week, the 8th week, and the 12th week showed statistically significant increases in morphine equivalent requirements as time passed to achieve pain control (Table 2).

Table 1. *Basic demographic characteristics among the studied patients in both groups.*

	CPN20 n = 16	CPN40 n = 16	d	95% C.I.	*P* value[α]
Age (years, Mean ± SD)	54.94 ± 5.66	57.38 ± 7.15	-0.3784	-1.0775, 0.3207	0.294
Gender, n (%)					
Male	6 (37.5%)	8 (50.0%)	0.254	-0.4417, 0.9497	0.476
Female	10 (62.5%)	8 (50.0%)			
Chronic illnesses, n (%)					
Hypertension	6 (37.5%)	7 (43.8%)	0.1285	-0.5651, 0.8222	0.719
Diabetes	5 (31.3%)	6 (37.5%)	0.1308	-0.5629, 0.8245	0.710
HCV	8 (50.0%)	4 (25.0%)	-0.5345	-1.2397, 0.1707	0.144
Bronchial asthma	0 (0.0%)	1 (6.3%)	1.8454	1.018, 2.6728	0.310
COPD	5 (31.3%)	3 (18.8%)	-0.2915	-0.9882, 0.4051	0.414
Cancer type, n (%)					
Pancreas	11 (68.8%)	12 (75.0%)	0.1383	-0.5555, 0.832	0.694
Liver	5 (31.3%)	3 (18.8%)	-0.2915	-0.9882, 0.4051	0.414
Stomach	0 (0.0%)	1 (6.3%)	1.8454	1.018, 2.6728	0.310
Cancer diagnosis confirmation, n (%)					
Radiological	16 (100%)	16 (100%)	N/A[$]		N/A[$]
Biopsy	11 (68.8%)	13 (81.3%)	0.2919	-0.4047, 0.9886	0.414
Presence of metastasis, n (%)					
Liver	3 (18.8%)	2 (12.5%)	-0.1741	-0.8683, 0.5202	0.626
Bone	2 (12.5%)	1 (6.3%)	1.2204	0.4657, 1.9751	0.544
Brain	0 (0.0%)	2 (12.5%)	0.5345	-0.1707, 1.2397	0.144
Treatment received, n (%)					
Radiotherapy	2 (12.5%)	2 (12.5%)	0	-0.693, 0.693	1
Chemotherapy	11 (68.8%)	12 (75.0%)	0.1383	-0.5555, 0.832	0.694
Surgery	4 (25.0%)	5 (31.3%)	0.1404	-0.5534, 0.8342	0.694
Site of pain, n (%)					
Upper abdominal only	10 (62.5%)	8 (50.0%)	-0.254	-0.9497, 0.4417	0.476
Upper abdominal plus back pain	6 (37.5%)	8 (50.0%)			0.476

[α] between both groups, the difference between the 2 groups is considered statistically significant if $P < 0.05$

[$] Not applicable as no statistics were computed because all patients in both groups had radiological confirmation of the tumor.

n = number; SD = standard deviation; d: standardized mean difference effect size; C.I: confidence interval

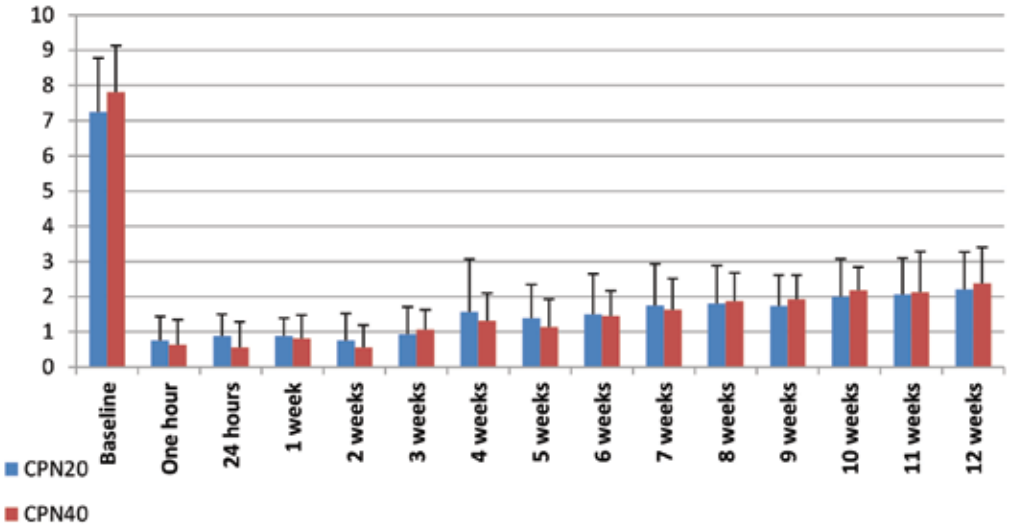

Fig. 3. *Reported scores of visual analog scale in the 2 study groups at different time points.*

Table 3 shows a comparison between the 2 groups regarding the total FACT-G scores (the higher the score, the better the outcome), the scores of the physical well-being domain in QOL assessment (the lower the score, the better the outcome), which includes assessment of patient's energy and physical impairment of function, the scores of the social/family well-being domain in QOL assessment (the higher the score, the better the outcome) which assesses the interaction of patient's family and friends to the illness, the scores of the emotional-wellbeing domain in the QOL assessment (the lower the score, the better the outcome) which evaluates the patient's coping with the disease and states of hope and fear of death and the scores of the functional well-being domain in the QOL assessment (the higher the score, the better the outcome) which measures the patient's sleep and work cycles, and his enjoyment of life activity.

There was no statistically significant difference between the study groups regarding all these domains at all time points (*P* value > 0.05). The scores of most time points in all domains were different significantly when compared to the baseline readings in both groups, with the tendency to decline over time in both groups approaching the baseline values.

No statistically significant difference was found between both groups regarding the incidence of post-operative complications. Hypotension occurred in 2 patients in the CPN20 group and 3 patients in the CPN40 group (RR = 0.6667, 95% C.I = 0.1281, 3.4698, *P* value =

Table 2. *Reported daily opioid consumption in milligrams of morphine equivalent doses in the two study groups at different time points.*

	CPN20		CPN40		*P* value[α]
	Mean ± SD	N	Mean ± SD	N	
Baseline	120 ± 28.98	16	121.88 ± 29.93		0.855
After procedure by:					
1 week	21.56 ± 13.38 [Ω]	16	20.63 ± 13.28 [Ω]	16	0.808
2 weeks	24.38 ± 10.78 [Ω]	16	23.44 ± 10.91 [Ω]	16	0.769
3 weeks	30 ± 17.32 [Ω]	16	29.06 ± 15.94 [Ω]	16	0.813
4 weeks	44.06 ± 30.73 [ΩΤ]	16	35.62 ± 24.41 [ΩΤ]	16	0.390
5 weeks	55.31 ± 53.31 [Ω]	16	37.5 ± 22.58 [Ω]	16	0.227
6 weeks	53.44 ± 40.61 [Ω]	16	42.19 ± 22.06 [Ω]	16	0.551
7 weeks	60 ± 39.49 [Ω]	16	53.44 ± 47.43 [Ω]	16	0.309
8 weeks	60 ± 32.07 [ΩΤΔ]	15	60 ± 42.43 [ΩΤΔ]	16	0.705
9 weeks	72 ± 31.67 [Ω]	15	75 ± 47.75 [Ω]	16	0.759
10 weeks	76 ± 27.46 [Ω]	15	75 ± 28.98 [Ω]	16	0.800
11 weeks	92 ± 26.51 [Ω]	15	90 ± 28.98 [Ω]	16	0.802
12 weeks	100.7 ± 30.25[ΩΤΔβ]	14	99.38 ± 30.43[ΩΤΔβ]	16	0.914

[α] between both groups, the difference between the 2 groups is considered statistically significant if $P < 0.05$; [Ω] indicates a statistically significant difference compared to the baseline in the same group with *P* value < 0.05; [Τ] indicates a statistically significant difference compared to the data of the first week after the procedure in the same group with *P* value < 0.05; [Δ] indicates a statistically significant difference compared to the data of the 4th week after the procedure in the same group with *P* value < 0.05; [β] indicates a statistically significant difference compared to the data of the 8th week after the procedure in the same group with *P* value < 0.05.

Table 3. *Reported total scores of the functional assessment of cancer therapy general questionnaire (FACT-G) in both groups at different time points.*

	CPN20		CPN40		*P*
	Mean ± SD	n	Mean ± SD	n	Value[α]
Total scores of the FACT-G questionnaire					
Baseline	27.93 ± 3.21	16	27.75 ± 3.45	16	0.875
After procedure by:					
1 week	66.06 ± 5.41 $^{\Omega}$	16	66.37 ± 4.98 $^{\Omega}$	16	0.925
4 weeks	61.81 ± 5.21 $^{\Omega\text{Ŧ}}$	16	59.56 ± 3.28 $^{\Omega\text{Ŧ}}$	16	0.167
8 weeks	53.00 ± 4.29 $^{\Omega\text{Ŧ}\Delta}$	15	52.93 ± 4.66 $^{\Omega\text{Ŧ}\Delta}$	16	0.969
12 weeks	42.50 ± 3.11$^{\Omega\text{Ŧ}\Delta\beta}$	14	40.31 ± 3.97$^{\Omega\text{Ŧ}\Delta\beta}$	16	0.137
The physical domain in the FACT-G questionnaire					
Baseline	22.5 ± 1.93	16	22.6 ± 1.93	16	0.787
After procedure by:					
1 week	12.25 ± 2.62 $^{\Omega}$	16	12.5 ± 2.68 $^{\Omega}$	16	0.849
4 weeks	13.56 ± 2.53 $^{\Omega\text{Ŧ}}$	16	14.19 ± 2.58 $^{\Omega}$	16	0.492
8 weeks	15.67 ± 2.55 $^{\Omega\text{Ŧ}}$	15	15.56 ± 2.66 $^{\Omega}$	16	0.912
12 weeks	15.57 ± 2.74 $^{\Omega\text{Ŧ}}$	14	15.81 ± 2.51 $^{\Omega}$	16	0.933
The social domain in the FACT-G questionnaire					
Baseline	14 ± 2.48	16	14.56 ± 2.50	16	0.505
After procedure by:					
1 week	18.31 ± 2.49 $^{\Omega}$	16	18.12 ± 2.42 $^{\Omega}$	16	0.831
4 weeks	18.56 ± 2.33 $^{\Omega}$	16	17.5 ± 2.33 $^{\Omega}$	16	0.175
8 weeks	16.47 ± 2.87 $^{\text{Ŧ}}$	15	16.31 ± 2.55	16	0.842
12 weeks	15.71 ± 1.14 $^{\text{Ŧ}}$	14	15.25 ± 1.65 $^{\text{Ŧ}}$	16	0.385
The emotional domain in the FACT-G questionnaire					
Baseline	22.06 ± 1.43	16	22.25 ± 1.48	16	0.7
After procedure by:					
1 week	10.94 ± 1.98 $^{\Omega}$	16	10.37 ± 2.31 $^{\Omega}$	16	0.411
4 weeks	13.68 ± 2.06 $^{\Omega\text{Ŧ}}$	16	14.5 ± 2.22 $^{\Omega\text{Ŧ}}$	16	0.321
8 weeks	14.86 ± 1.99 $^{\Omega\text{Ŧ}}$	15	14.75 ± 2.26 $^{\Omega\text{Ŧ}}$	16	0.826
12 weeks	19.36 ± 1.34$^{\Omega\text{Ŧ}\Delta\beta}$	14	19.93 ± 1.34$^{\Omega\text{Ŧ}\Delta\beta}$	16	0.245
The functional domain in the FACT-G questionnaire					
Baseline	6.56 ± 2.25	16	6.06 ± 2.21	16	0.53
After procedure by:					
1 week	19.5 ± 2.19 $^{\Omega}$	16	19.13 ± 2.47 $^{\Omega}$	16	0.653
4 weeks	18.5 ± 2.58 $^{\Omega}$	16	18.75 ± 2.54 $^{\Omega}$	16	0.717
8 weeks	15.07 ± 2.08 $^{\Omega\text{Ŧ}\Delta}$	15	14.93 ± 2.43 $^{\Omega\text{Ŧ}\Delta}$	16	0.888
12 weeks	9.86 ± 2.48$^{\Omega\text{Ŧ}\Delta\beta}$	14	8.81 ± 2.69$^{\Omega\text{Ŧ}\Delta\beta}$	16	0.280

[α] between both groups, the difference between the 2 groups is considered statistically significant if $P < 0.05$; $^{\Omega}$ indicates a statistically significant difference compared to the baseline in the same group with *P* value < 0.05; $^{\text{Ŧ}}$ indicates a statistically significant difference compared to the data of the first week after the procedure in the same group with *P* value < 0.05; $^{\Delta}$ indicates a statistically significant difference compared to the data of the 4th week after the procedure in the same group with *P* value < 0.05; $^{\beta}$ indicates a statistically significant difference compared to the data of the 8th week after the procedure in the same group with *P* value < 0.05.

0.626), while diarrhea occurred for one patient in the CPN20 group and 2 patients in the CPN40 group (RR = 0.5, 95% C.I = 0.0502, 4.9784, *P* value = 0.544). All these complications were transient and self-limited. No other complications were recorded in both groups during the follow-up period.

Discussion

Pain is the symptom that most cancer patients fear. Up to 50% of patients undergoing cancer treatment have debilitating pain, which increases to 90% of patients with advanced cancer (16).

It is thought that CPN reduces pain by interrupting the afferent transmission of nociception and that this intervention may also indirectly modify the stress response and illness-related behavior (17).

Ultrasound has been described as a simple and cost-effective modality for use with CPB and permits real-time visualization of the aorta and visceral arteries, and enables the diffusion of the neurolytic agent to be viewed without the aid of contrast media (18).

Visual Analog Scores

Our results showed that the mean values of VAS scores were maintained below 3 centimeters in both groups. There was no significant difference between the 2 groups at any time point of follow up; however, the difference was statistically significant compared to the baseline in both groups.

Similarly, Amr and Makharita (19) performed CPN by injecting 40 mL of 70% alcohol under fluoroscopic guidance to compare the procedure effect before and after a short period of adjusting medical management and followed their patients for one year after enrollment. They reported reduced VAS scores, which remained less than 4 in the group of patients who underwent a short period of medical pain control until the end of the follow-up period.

On the other hand, Dolly and colleagues (12) did a small comparative study to evaluate the efficacy of injecting 20 mL, 30 mL, or 40 mL of 70% alcohol in achieving adequate CPN and reported VAS scores of less than 4/10 in the patients who received 40 mL until the end of a 16 weeks follow-up period whereas this level was maintained only for 8 weeks in those receiving 20 mL of alcohol. A closer look at the reported data helps in explaining the difference between the groups of their study. At 8 weeks, the mean daily morphine consumption in the 20 mL group was only 20 mg per day. Surprisingly, they reported a mean of 84 mg daily

morphine starting from the 12th week in this group until the 16th week despite a reported VAS of more than 8/10 during this period which reflects inadequate medical management and very slow increments in opioid dosing in response to increased pain. Adjustment of medical management is of crucial importance in controlling pain in this patient population, and early success of any interventional procedures should not deprive the patients of optimal medical dosing of opioids.

Complete pain relief until time of death was reported to be 10% to 24% using CPN alone, and the outcome improves to 80% to 90% when combined with adequate medical therapy. (20). This can be explained more by reviewing many other studies which have shown that pain improvement using 20 mL (or even less) of alcohol for celiac neurolysis is comparable to that achieved by the use of 40 mL.

The authors of an Italian study (21) divided 24 patients into 2 equal groups: group 1 received a fluoroscopic guided CBN with 14 mL absolute alcohol after local anesthetic injection, and the control group received only local anesthetic injection. They reported complete relief of pain until death in 80% of patients with adequate dosing of medications.

Tewari and colleagues (22) retrospectively analyzed data from patients who underwent CPN with 20 mL absolute alcohol using single needle transaortic technique and found reduced pain scores until 3 months after the block, with a tendency to increase gradually approaching the baseline readings by 6 months after the block.

Bhatnagar and colleagues (8) also injected 20 mL of 50% alcohol in 60 patients using an anterior single needle or 2 needles guided by ultrasound guidance and reported markedly reduced pain scores during 3 months of follow-up.

Moreover, a metanalysis performed on 6 case series by Nagels (10) included a total of 209 patients who received endoscopic CPN with 20 mL 98% alcohol reporting a significant decrease in pain scores during the follow-up period.

Opioid Consumption

Our results demonstrated the efficacy of the CPN to decrease morphine equivalent requirements for a short period after the procedure compared to the baseline. However, there was no significant difference between both groups during the study period.

Several studies have reported a lower morphine consumption in patients who received CPN with different volumes of alcohol ranging from 14 mL to 60 mL when compared to standard medical management (21-25).

Dolly and colleagues (12) compared the use of different volumes of alcohol for CPN. They reported a significant reduction of morphine consumption in both groups that received 20 mL or 40 mL of 70% alcohol. They also reported a successful total withdrawal of opioids from 47% of participants.

Similarly, Shwita and colleagues (15) performed a retrocrural CPN using 40 mL of 70% alcohol on 30 patients and reported a large decrease in strong opioid consumption during the period of follow-up.

One point to be noted in this study is that the reported doses of morphine were relatively higher in comparison to our results which might be due to the higher baseline morphine requirements in their population.

Yoon and his colleagues (26) found that a pre-procedure low opioid dose is an independent predictor of a better outcome . Similarly, Erdek and colleagues (27) found in a retrospective study that pre-procedural opioid dose had the strongest association with successful outcomes following CPN. This may be attributed to the fact that increased opioid requirements indicate a more severe disease state, the effect of large opioid doses on mood and coping skills deterioration, and the development of opioid induced hyperalgesia.

Quality of Life

The present study showed that the QOL response was short-lived and deteriorated significantly afterward.

Wong et al (14) compared alcohol CPN versus systemic analgesic therapy. They found a slight improvement in the QOL after 1 week using the FACT-PA scale, which was not statistically significant compared to the baseline. They reported a significant difference between both groups regarding the physical and functional subscales, with no difference regarding the other scales or the total QOL score.

Similarly, Molnar and colleagues (28) used 40 mL of 70% alcohol for CPN in 16 patients with pancreatic cancer. They used the SF-26 questionnaire for QOL assessment and found improvement in 5 dimensions out of 8 after 35 days of the block compared to the baseline.

Similarly, several studies have assessed the impact of CPN on the QOL using different questionnaires. The main findings were improvement of the QOL for a short period ranging from 2 weeks to 3 months, followed by gradual deterioration over the rest of the follow-up period (15,19,24,25,29,30).

A well-documented fact in this context is that chemical neurolysis does not completely disrupt the nerve cells, and the destructed cells tend to regrow. Also, there is a risk of deafferentation pain arising from abnormal regeneration after CPN. Vranken et al (31) did an autopsy on 2 cases of cancer pancreases receiving 40 mL of 70% alcohol through catheters. The first showed pain reduction for 2 months and received another injection of 40 mL 70% alcohol, and the second received the repeated block after 2 weeks of the first procedure. Microscopically there was evidence of affected neurons, but interestingly the greater amount of CP neurons and ganglia showed normal morphology.

Procedure-Related Side Effects

Hypotension was responsive to fluid management, and diarrhea was self-limited in all patients without long-term complications. A preloading with fluids may contribute to the lower incidence of hypotension after CPN, as reported by Marcy and colleagues (32).

The fact that we injected alcohol in front of the aorta might also be a reason for the lower rate of these side effects. Ischia et al found less orthostatic hypotension during the transaortic approach compared to other posterior approaches for CPN. This was explained by the fact that neurolytic agent injection anterior to the aorta limits its spread in the psoas compartment, which contains the sympathetic chain (20).

Several studies concluded that these complications were mild and responded to conservative management and that there was no difference in incidence or severity depending on the volume of injected alcohol (18,26,33-35).

Finally, there are several limitations of this study. This was a single-center study with a relatively small sample size. Further prospective, multicenter, randomized, and controlled studies with a larger sample size are required to confirm the effects in this study.

Conclusion

During ultrasound-guided CPN for patients with inoperable upper abdominal cancers who failed medical management, a volume of 20 mL is as effective as 40 mL of 70% alcohol regarding pain control, opioid consumption, QOL, and procedure-related complications.

Acknowledgments

We would like to show thanks and appreciation to every patient who participated in our work. Deep thanks to our colleagues in the Suez Canal university hospital. Special thanks to our colleague Wesam Fawzy, MD, for her help in statistical work.

This study was approved by Suez Canal University's Institutional ethical review board committee (research #3354) on 03/01/2018, and written informed consent was obtained from all patients participating in the trial. The trial was registered before enrolment of the first patient at the Pan African Clinical Trial Registry (PACTR) (www.pactr.org) database (PACTR201803003212106, Date of registration: 22 March 2018). This manuscript adheres to the applicable CONSORT guidelines.

Author's Contribution

Mohamed E. Abdel-Ghaffar, MD: This author helped in preparing the concept of the research, design, data acquisition, and final editing of the paper.

Salah A. Ismail, MD: This author helped in preparing the concept of the research, design, clinical work,dData acquisition, and final editing of the paper.

Reda A.Ismail, MD: This author helped in the definition of intellectual content, literature search, manuscript review, and manuscript editing.

Mostafa M. Ebrahim, MD: This author helped in literature search, clinical work, and data acquisition.

Mohamed E. Abuelnaga, MD: This author helped in literature search, clinical work, manuscript preparation, and manuscript review.

References

1. Sehgal S, Ghaleb A. Neurolytic celiac plexus block for pancreatic cancer pain: A review of literature. *Indian J Pain* 2013; 27:121-131.
2. Wyse JM, Chen YI, Sahai AV. Celiac plexus neurolysis in the management of unresectable pancreatic cancer: When and how? *World J Gastroenterol* 2014; 20:2186-2192.
3. Bahn BM, Erdek MA. Celiac plexus block and neurolysis for pancreatic cancer. *Curr Pain Headache Rep* 2013;17:310.
4. Eisenberg E, Carr D, Chalmers T. Neurolytic celiac plexus block for treatment of cancer pain: A meta-analysis. *Anesth Analg* 1995; 80:290-295.
5. Ghai A, Kumar H, Karwasra R, Kad N, Rohilla S, Parsad S. Ultrasound guided celiac plexus neurolysis by anterior approach for pain management in upper abdominal malignancy: Our experience. *APICare* 2019;274-281.
6. Dhamija E, Khandelwal I, Bhatnagar S, Thulkar S. A systematic approach to give bedside ultrasound-guided celiac plexus block. *Indian J Pain* 2017; 31: 80-85.
7. Caratozzolo M, Lirici M, Consalvo M, Marzano F, Fumarola E, Angelini L. Ultrasound-guided alcoholization

of celiac plexus for pain control in oncology. *Surg Endosc* 1997; 11:239-244.

8. Bhatnagar S, Joshi S, Rana S, Mishra S, Garg R, Ahmed SM. Bedside ultrasound-guided celiac plexus neurolysis in upper abdominal cancer patients: A randomized, prospective study for comparison of percutaneous bilateral paramedian vs. unilateral paramedian needle-insertion technique. *Pain Pract* 2014; 14:E63-E68.
9. Akins EW, Hawkins IF, Mladinich C, Tupler R, Siragusa RJ, Pry R. The blunt needle: A new percutaneous access device. *AJR Am J Roentgenol* 1989; 152:181-182.
10. 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.
11. Gimeno-García A, Elwassief A, Paquin S, Sahai A. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. *Endoscopy* 2012; 44:E267.
12. Dolly A, Singh S, Prakash R, Bogra J, Malik A, Singh V. Comparative evaluation of different volumes of 70% alcohol in celiac plexus block for upper abdominal malignsancies. *South Asian J Cancer* 2016; 5:204-209.
13. Conroy T, Mercier M, Bonneterre J, et al. French version of FACT-G: Validation and comparison with other cancer-specific instruments. *Eur J Cancer* 2004; 40:2243-2252.
14. Wong GY, Schroeder DR, Carns PE, et al. 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.
15. Shwita AH, Amr YM, Okab MI. Comparative study of the effects of the retrocrural celiac plexus block versus splanchnic nerve block, C-arm guided, for upper gastrointestinal tract tumors on pain relief and the quality of life at a six-month follow up. *Korean J Pain* 2015; 28:22-31.
16. Cherny NI, Portenoy RK. The management of cancer pain. *CA Cancer J Clin* 1994; 44:263-303.
17. Kumar SP. Cancer pain: a critical review of mechanism-based classification and physical therapy management in palliative care. *Indian J Palliat Care* 2011; 17:116-126.
18. Bhatnagar S, Thulkar S, Dhamija E, Khandelwal I, Nandi R, Chana G. Evaluation of outcomes of ultrasound guided celiac plexus neurolysis using immediate post procedure computed tomography: An observational study. *Indian J Gastroenterol* 2017; 36:282-288.
19. Amr YM, Makharita MY. Comparative study between 2 protocols for management of severe pain in patients with unresectable pancreatic cancer: One-year follow-up. *Clin J Pain* 2013; 29:807-813.
20. 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.
21. Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia I. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *Br J Surg* 1998; 85:199-201.
22. Tewari S, Agarwal A, Dhiraaj S, et al. Comparative evaluation of retrocrural versus transaortic neurolytic celiac plexus block for pain relief in patients with upper abdominal malignancy: A retrospective observational study. *Indian J Palliat Care* 2016; 22:301-306.
23. Kawamata M, Ishitani K, Ishikawa K, et al. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain* 1996; 64:597-602.
24. Zhang CL, Zhang TJ, Guo YN, et al. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. *Dig Dis Sci* 2008; 53:856-860.
25. Stefaniak T, Basinski A, Vingerhoets A, et al. A comparison of two invasive techniques in the management of intractable pain due to inoperable pancreatic cancer: Neurolytic celiac plexus block and videothoracoscopic splanchnicectomy. *Eur J Surg Oncol* 2005; 31:768-773.
26. Yoon DM, Yoon KB, Baek IC, Ko SH, Kim SH. Predictors of analgesic efficacy of neurolytic celiac plexus block in patients with unresectable pancreatic cancer: The importance of timing. *Support Care Cancer* 2018; 26:2023-2030.
27. Erdek MA, Halpert DE, Fernández MG, Cohen SP. Assessment of celiac plexus block and neurolysis outcomes and technique in the management of refractory visceral cancer pain. *Pain Med* 2010; 11:92-100.
28. Molnár I, Hegyi G, Zsom L, et al. Celiac plexus block increases quality of life in patients with pancreatic cancer. *J Pain Res* 2019; 12:307-315.
29. Mercadante S, Catala E, Arcuri E, Casuccio A. Celiac plexus block for pancreatic cancer pain: Factors influencing pain, symptoms and quality of life. *J Pain Symptom Manage* 2003; 26:1140-1147.
30. Kambhampati S, Sugar EA, Herman JM, Erdek MA, Shin EJ, Laheru DA. A comparison of percutaneous and endoscopic-guided celiac plexus block/neurolysis in pancreatic cancer patients. *JCO Oncol Pract* 2017: E15767.
31. Vranken J, Zuurmond W, Van Kemenade F, Dzoljic M. Neurohistopathologic findings after a neurolytic celiac plexus block with alcohol in patients with pancreatic cancer pain. *Acta Anaesthesiol Scand* 2002; 46:827-830.
32. Marcy PY, Magné N, Descamps B. Coeliac plexus block: Utility of the anterior approach and the real time colour ultrasound guidance in cancer patient. *Eur J Surg Oncol* 2001; 27:746-749.
33. LeBlanc JK, Al-Haddad M, McHenry L, et al. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: One injection or two? *Gastrointest Endosc* 2011; 74:1300-1307.
34. Bhatnagar S, Khanna S, Roshni S, et al. Early ultrasound-guided neurolysis for pain management in gastrointestinal and pelvic malignancies: An observational study in a tertiary care center of urban India. *Pain Pract* 2012; 12:23-32.
35. Mohamed RE, Amin MA, Omar HM. Computed tomography-guided celiac plexus neurolysis for intractable pain of unresectable pancreatic cancer. *Egypt J Radiol Nucl Med* 2017; 48:627-637.