Endoscopic ultrasound-guided celiac plexus neurolysis for treatment of hepatocellular carcinoma-related abdominal pain

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Received 29 January 2019
Accepted 17 February 2019

Kasr Al Ainy Medical Journal 2018, 24:142–148

Background
Overall, 20–50% of patients with hepatocellular carcinoma (HCC) present at advanced stage where palliative treatment is the only reasonable management. Pain in HCC is a significant factor of morbidity, and celiac plexus neurolysis demonstrated good results in relief of pain as a result of pancreatic cancer; however, there are no studies concerning its use in management of HCC.
Patients and methods
A total of 30 patients with advanced stage HCC complaining of moderate to severe abdominal pain, requiring opioid analgesics to control, scored their abdominal pain according to the Numeric Rating Scale-11 before the procedure and were re-assessed every 2 weeks for 2 months.
Results
This study included 30 patients, comprising 24 men and six women, with a mean age of 61.73±7.9 years. A significant correlation between older age and better BCLC staging and pain reduction was found (P=0.045 and 0.08, respectively), whereas there is no significant correlation between pain reduction and clinical manifestations and medical history. There is a significant reduction in pain score after the procedure. Median pain score was significantly lower than pre-endoscopic median pain score, with a P value less than 0.001.
Conclusion
Endoscopic ultrasound-celiac plexus neurolysis should be a potential choice in patients with moderate to severe abdominal pain in patients with HCC who are not considered for therapeutic intervention.

Keywords:
celiac plexus neurolysis, endoscopic ultrasound, hepatocellular carcinoma

Kasr Al Ainy Med J 24:142–148

1687-4625

Introduction

Hepatocellular carcinoma (HCC) is the third most frequent cause of cancer death worldwide. People with early-stage HCC may benefit from potentially curative therapies. Unfortunately, a significant proportion of patients are diagnosed at advanced stages. Therefore, these patients have bad prognosis, and the ablative treatment options are limited [1].

In Egypt, HCC is the second most common cancer in men and the sixth most common cancers in women. There was nearly a two-fold increase of the proportion of HCC among patients with chronic liver disease in Egypt from 4% in 1993 to 7.3% in 2003 [2].

There is a wide variation in the clinical presentation of HCC [3]. Overall, 50 to 20% of patients with HCC present at an advanced stage, with median survival less than 3–4 months. As a result of this poor prognosis, palliative treatment is the only reasonable management as no tumor-directed therapy is applicable. Pain in HCC can be from either the tumor itself or a complication of intervention, yet it is very common and is a significant factor of morbidity. The pain of HCC has a tendency to be most prominent in the right upper quadrant and described as deep, aching, sharp, or stabbing [4].

In hepatic patients, the elimination and the metabolism of most analgesics, including paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids, can be impaired. As a result, drugs accumulate and adverse effects may increase. Moreover, liver dysfunction can significantly change pharmacodynamics of the drugs. An example is enhanced sensitivity to opioids, which can cause cerebral dysfunction or exacerbate pre-existing hepatic encephalopathy [5]. On the contrary, drugs themselves can also cause liver dysfunction. Many drugs including analgesics can cause liver injury [6].

The celiac 'plexus' provides nerve supply for organs in the upper abdomen [7]. Celiac plexus neurolysis (CPN) was initially introduced as an intraoperative procedure for chemical destruction of the CPN in 1914. Following this, it has been carried out under radiographic, fluoroscopic, computed tomography (CT), or ultrasonographic imaging guidance [8–10].

Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) was assessed by several studies in pancreatic cancer for pain management and demonstrated good results with relief of pain as a result of pancreatic cancer in ~80% of patients [8]. However, there are no studies concerning its use in the management of abdominal pain in HCC despite that the celiac plexus also innervates the liver.

In this study, we tried to evaluate the efficacy and safety of EUS-CPN as a palliative procedure in managing abdominal pain associated with HCC.

Patients and methods

Study design

This is a prospective, observational study that was performed on patients selected from attendees of the Hepatology and Early Detection of HCC Outpatient Clinics or admitted patients at Gastroenterology and Hepatology Unit, Specialized Medical Hospital (SMH), Mansoura University, Egypt.

Patients

This study included 30 patients diagnosed with HCC and complaining of moderate to severe abdominal pain requiring opioid analgesics to control and are not eligible for tumor-directed therapies. Patients with uncorrectable clinically significant coagulopathy; conditions altering upper gastrointestinal tract (GIT) anatomy, for example, gastric bypass making echoendoscope access not possible; or history of hepatic encephalopathy were excluded.

Each patient was subjected to full medical history and clinical assessment.

Laboratory assessment

Liver and renal functions were examined and then liver function state was assessed by Child–Turcotte–Pugh (CTP) classification to evaluate the outcome of liver cirrhosis.

Imaging studies

Abdominal ultrasound and triphasic CT abdomen were done with specific diagnostic radiological criteria of HCC (early enhancement in hepatic arterial phase and washout in delayed and portal phases) and specifically commenting on tumor site, size, lymph node involvement, and metastasis.

Pain assessment

Patients scored their pain on a scale from 0 to 10 (The Numeric Rating Scale-11) before the procedure and were re-assessed every 2 weeks for 2 months and then monthly till 4 months after the procedure. According to the degree of pain reduction, patients were divided into three groups and compared as follows:

Group 1: patients with less than 30% pain reduction.
Group 2: patients with 30–50% pain reduction.
Group 3: patients with more than 50% pain reduction.

Endoscopic ultrasound-guided celiac plexus neurolysis

EUS-guided CPN was done under general anesthesia using propofol while the patient is in left lateral decubitus position.

The EUS (EG-3870UTK, linear array; Pentax, Germany) was introduced into the stomach. After this, the EUS was rotated in clockwise direction toward the posterior wall of the stomach with gradual withdrawal till the abdominal aorta was visualized in the longitudinal plane, and by following the aorta, the origin of the celiac artery could be pinpointed.

Next, 22-G needle was introduced through the operating channel of the echoendoscope. The needle tip was advanced under real-time EUS guidance, to a site just above the origin of the celiac artery. To confirm that no vessel has been punctured, aspiration was done using a syringe, ensuring that there is no backflow of blood, and then 3 ml of bupivacaine 0.5% was injected. After that, 15–20 ml of alcohol (95%) was injected using another syringe. With the injection of alcohol, an echogenic cloud was visualized on EUS around the area of the injection.

Statistical analysis

Data were entered and statistically analyzed using the statistical package for the social sciences (SPSS) version 20 (SPSS Inc, Chicago, IL, USA). Qualitative data were described as numbers and percentages. χ^2-Test was used for comparison, and Monte Carlo test was used when more than 20% of cells have count less than 5.

Quantitative data were described as median and range for nonparametric variables and mean and SD for

parametric ones after testing normality by Kolmogorov–Smirnov test. For nonparametric variables, Kruskal–Wallis and Mann–Whitney tests were used for comparison between groups and Wilcoxon for paired comparison between two periods in the same group. For parametric variables, one-way analysis of variance test was used for comparison between groups with post-hoc least significant difference for pairwise comparison. Spearman correlation was used to correlate nonparametric continuous variables. *P* value up to 0.05 was considered to be statistically significant. All tests were two-tailed.

Table 1 Demographic characteristics of the studied cases

	N=30 [*n* (%)]
Age (years)	
Mean±SD	61.73±7.9
Minimum–maximum	49.0–80.0
Sex	
Male	24 (80.0)
Female	6 (20.0)
Hypertension	2 (6.6)
DM	6 (20)
Smoking	6 (20)

Table 2 Medical history among studied cases

	N=30 [*n* (%)]
History of esophageal variceal bleeding and intervention	6 (20)
Ascites	13 (43.3)
Jaundice	12 (40)
History of hepatic encephalopathy	0

Table 3 Distribution of cases according to tumor characters

	N=30 [*n* (%)]
Portal vein thrombosis	14 (46.7)
LN or extraspread	3 (10.0)
Biliary invasion	4 (13.3)
CTP score	
A	15 (50)
B	9 (30)
C	6 (20)
BCLC staging	
C	18 (60.0)
D	12 (40.0)
Focal lesion number	
Single	9 (30.0)
<3	4 (13.3)
>3	17 (56.7)
Focal lesion site	
Right	12 (40.0)
Left	5 (16.7)
Diffuse	13 (43.3)

Ethics

The study protocol was investigated and approved by medical ethics research team, Faculty of Medicine, Mansoura University. Every case, after guaranteeing privacy, gave informed written consent.

Results

This study included 30 patient, comprising 24 men and six women, with mean age of 61.73±7.9 years. The demographic characteristics and medical history of studied cases are shown in Tables 1 and 2, respectively. Table 3 shows the tumor characteristics of the studied cases. The laboratory results of the studied cases are shown in Table 4.

The distribution of cases according to median pain score before endoscopy and at 2, 4, 6, 8, 12 and 16 weeks after endoscope and number of patients alive is shown in Table 4. Table 5 shows the distribution of cases according to degree of pain reduction. Regarding demographic data, there was no statistical significance among the three groups except for age where response was more pronounced in older age groups (Table 6). Table 8 shows positive correlation between age and pain reduction. The pain score significantly declined in the postendoscopy period as shown in Table 7 and Fig. 1. Table 8 shows that the median response time was 14 days, median survival was 36 days, and median pain-free period was 32 days.

Table 4 Distribution of studied cases according to median pain score and number of patients alive

Pain score	Median (minimum–maximum)	Number of patients alive
Before endoscopy	9.0 (5.0–10.0)	30
After 2 weeks	3.0 (0.0–10.0)	30 (100)
After 4 weeks	2.0 (0.0–10.0)	21 (70)
After 6 weeks	1.0 (0.0–6.0)	16 (53.3)
After 8 weeks	1.5 (0.0–6.0)	12 (40.0)
After 12 weeks	1.5 (0.0–10.0)	8 (26.7)
After 16 weeks	2.0 (0.0–10.0)	5 (16.7)

Table 5 Distribution of patients according to degree of pain reduction

	N (%)
Group 1 (<30%)	**7** (**23.3**)
Group 2 (30–50%)	**2** (**6.7**)
Group 3 (>50%)	**21** (**70**)

Discussion

The incidence of HCC is increasing worldwide especially in endemic areas of hepatitis C virus (HCV) or hepatitis B virus (HBV) infection [11,12]. Egypt has one of the highest HCV prevalence worldwide [13], and up to 90% of HCC cases were attributed to HCV infection [14].

Pain in HCC can be from either the disease itself or a complication of intervention, yet independent of the reason, it is very common and is a noteworthy reason for disturbing quality of life. The pain of HCC tends to be most prominent in the right upper quadrant and described as deep, aching, sharp, or stabbing. Abdominal pain in HCC is mainly owing to visceral affection caused by a primary or metastatic tumor affecting the abdominal or pelvic viscera [4].

Table 6 Correlation between pain reduction score and laboratory, demographic, and clinical manifestations.

		Pain reduction
Age	*R*	0.446*
	P	0.014
Alanine aminotransferase	*R*	0.342
	P	0.065
Aspartate aminotransferase	*R*	0.171
	P	0.366
Platelets count ($\times 10^3$)	*r*	–0.060
	P	0.751
Hemoglobin level	*r*	–0.101
	P	0.595
Total leukocytic count ($\times 10^3$)	*r*	–0.155
	P	0.414
Focal lesion number	*r*	0.144
	P	0.447
Time to response	*r*	–0.147
	P	0.484
International normalized ratio	*r*	–0.101
	P	0.595
Serum creatinine	*r*	0.113
	P	0.550
Total bilirubin	*r*	–0.311
	P	0.074
Time to death	*r*	0.491
	P	0.008**
Serum albumin	*r*	0.369
	P	0.045

r, Spearman correlation coefficient. *statistical significance. **High statistical significance.

All types of analgesia can cause problems in advanced liver disease; however, expert opinion state that morphine and its derivatives are preferred, and fentanyl is an excellent choice in patients with hepatic dysfunction [4].

In this study, we examined a way of pain control that can be both effective and safe even in patients with terminal liver disease owing to HCC [Barcelona Clinic Liver Cancer (BCLC) stage C and D].

Our study included 30 patients, comprising 24 (80%) males and six (20%) females, with a mean age of 61.73 ±7.9 years (Table 1) which runs parallel to the mean age of 62 and 63 years in the studies conducted by Wiechowska-Kozlowska *et al.* [15] and LeBlanc *et al.* [16], respectively, who studied EUS-CPN in patients with pancreatic cancer .

However, most patient in our study were males in contrast to the aforementioned two studies, where males represented approximately half of the patient. This finding is consistent with the global epidemiology of HCC [17].

The possible explanation of more prevalent HCC in men than in women may be the differences in exposure to risk factors. However, sex hormones and other x-linked genetic factors may also be important. It has been speculated that androgens could modulate hepatocarcinogenesis and explain the higher incidence of HCC in men [2].

In this study, older patients had more pain reduction than younger patients. There was a significant association (P=0.045) and positive correlation (P=0.014, r=0.446) between pain reduction and increasing age (Table 6). This important note can be explained by the fact that older patients have few daily

Table 8 Time to response, time to death, and pain-free period

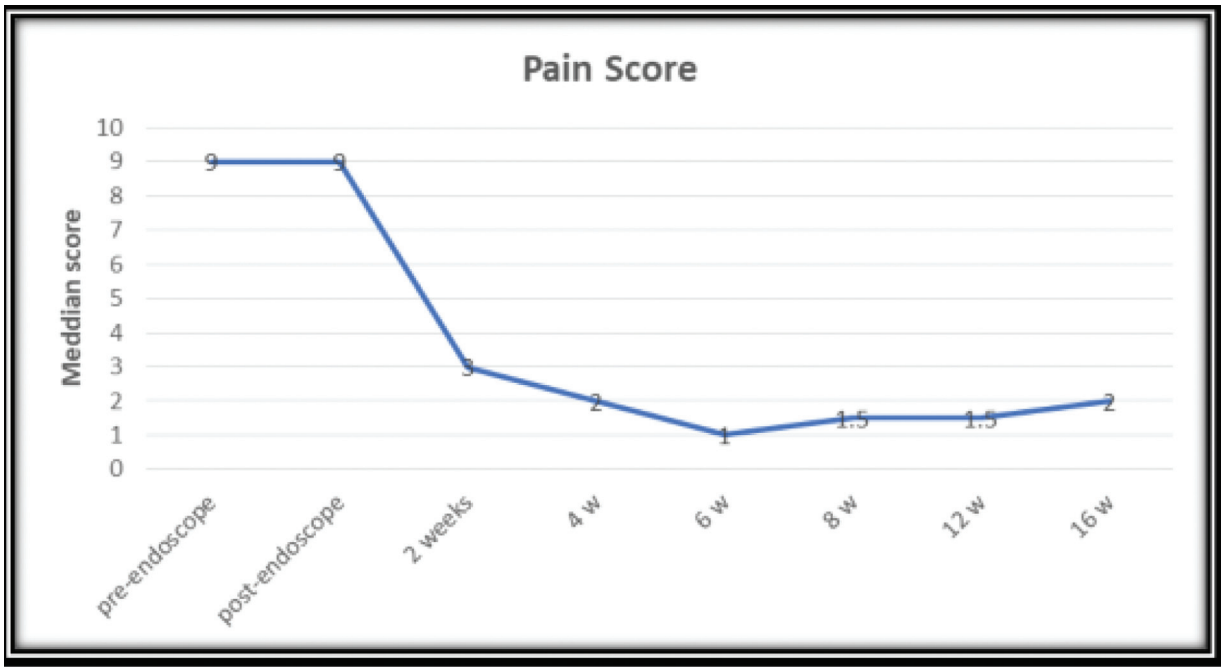
Time to response [median (minimum–maximum)] (days)	14.0 (0.0–14.0)
Time to death [median (minimum–maximum)] (days)	36.0 (15.0–117.0)
Pain-free period [median (minimum–maximum)] (days)	32.0 (1.0–105.0)

Table 7 Pain score change from before endoscopy till 16 weeks after

	Before endoscope	2 weeks after	4 weeks after	6 weeks after	8 weeks after	12 weeks after	16 weeks after
Pain score [median (minimum–maximum)	9.0 (5.0–10.0)	3.0 (0.0–10.0)	2.0 (0.0–10.0)	1.0 (0.0–6.0)	1.5 (0.0–6.0)	1.5 (0.0–10.0)	2.0 (0.0–10.0)
Wilcoxon signed rank test		$P<0.001$*	$P<0.001$*	$P<0.001$*	$P<0.001$*	P=0.016*	P=250

*statistical significance.

Figure 1



Median pain score over time following celiac plexus neurolysis. The figure shows reduced median pain score after the procedure and remained low throughout the follow-up period.

activities, so they subjectively feel more pain reduction because they can resume their usual daily activities whereas younger age group patients who are more active and cannot resume their normal daily activities even if they have the same degree of pain reduction, so they subjectively feel less improvement.

In our study, ascites and jaundice were present in 43.3 and 40.0% of patients, respectively. History of upper gastrointestinal (GI) bleeding and variceal intervention was present in 20% (Table 2).

These data are concomitant with the data from a study conducted by Gopal *et al*. [18] who found that patients with HCC presented with ascites in 46.7%, and the study by Shaker *et al*. [19] who reported jaundice in 26.3%, hepatic encephalopathy in 7.5%, and upper GI bleeding in 14% of patients. In this study, patients with hepatic encephalopathy were excluded to avoid postprocedure complication and allow better assessment of pain, which is not possible if patient is in hepatic encephalopathy.

Regarding this study, patients were classified according to CTP score and BCLC staging, and we found that 60% of patients were stage C according to BCLC staging and 40% were stage D (Table 3). The fact that all our patients are either stage C or D is because their performance status is affected by pain, which makes them feel unwell and become less active, leading to performance status ranging from 1 to 4, whereas earlier stages of BCLC staging (stage 0, A, and B) have performance status grade 0 (fully active and able to carry on all predisease performance without restriction), and also a large number of our patients have portal vein thrombosis, which affects their staging.

There was more significant pain reduction in stage C (71.4% of patient with pain reduction>50%) than stage D (28.6% of patients with pain reduction>50%), with significant *P* value (*P*=0.001). This indicates that earlier stage of HCC is a predictor of good pain response than late cases with more advanced disease.

In our study regarding hepatic focal lesions, most patients have multiple lesion 21 (70%), with diffuse pattern in both liver lobes, representing 43%, whereas right lobe lesions represented 40% and left lobe lesions represented 16.7%.

This goes hand in hand with the more common presentation of right hypochondrial pain, and this matches with a study by Abd-Elsalam *et al*. [20] who found that 52.5% of cases had multiple focal lesions, mostly in the right side. The high percentage of cases with diffuse HCC can be explained by inclusion criteria of patients who have more advanced disease with greater tumor burden causing pain (Table 3). However, there was no significant difference in pain reduction regarding site

and number of focal lesions. This is a good point favoring that all patients regardless of site, size, and number of lesions can be considered for EUS-CPN and there are no similar data regarding this to compare with regarding patients with HCC.

Some studies consider platelet count less than 50 000 or INR more than 1.5 as a contra-indication to EUS-CPN [15,21]. However, in this study, we performed the procedure in patients with platelet count ranging from 46 000 to 400 000 and INR ranging from 1.0 to 1.8 as long as the patient does not have history of bleeding tendency, and there is no clinical signs of coagulopathy. This is owing to the nature of our studied cases, as all of them are chronic hepatic patients with advanced HCC.

In this study, average pain score of 9 (range: 5–10) was observed in all patients before the procedure. One to two weeks following treatment, 21 (70%) patients had a reduction in pain by more than 50% of which 12 (40%) patients had complete resolution of pain (pain score 0 or 1) and completely stopped taking pain medications. Two (6.7%) patients had a reduction in pain by 30–50%. Lastly, seven (23.3%) patients had a pain reduction less than 30%, of which four (13.3%) had no response at all (Table 5).

Iwata *et al*. [22] found similar results where 68.1% of his patients with pancreatic cancer had successful pain relief, of which 36.2% had complete pain relief and 31.9% had insufficient pain relief. However, in this study, alcohol was injected using combination of central and lateral techniques.

It is obvious that not all patients had optimal response to CPN, which may be owing to partial destruction of nerve fibers in celiac plexus. As a result, continued transmission of pain stimuli is still possible, although reduced in most patients.

This is consistent with pathologic studies of the plexus following treatment. It is also reported that distribution of alcohol only on the left side of the celiac artery was a negative predictive factor for response detected by performing CT scan after the procedure and using ethanol-containing contrast medium. Ethanol was distributed only on the left side of the celiac plexus in a significantly greater number of patients in the insufficient-pain-relief group than in the successful-treatment group (46.7 vs. 6.3%, P=0.0025) [22].

Other explanations include technical difficulties owing to the presence of collaterals, early death of patient not allowing full evaluation of response, and single treatment session.

Reduction of pain was associated with improvement in emotional, functional, and physical well-being as well as marked improvement in sleep quality. Similar results were reported by LeBlanc *et al*. [16] and Seicean *et al*. [21].

Median pain score was 3 at week 2, which was significantly lower than pre-endoscopic median pain score, with a P value less than 0.001. This is consistent with Seicean *et al*. [21] who reported pre-endoscopic pain score to be 9±1.21 which was reduced to 5±2.47, with a P value of 0.001. The median pain score remained lower than the pre-endoscopic one throughout the follow-up period till 16 weeks, at which the median pain score was still low (Table 4 and Fig. 1).

These results also correspond to a reported median duration of pain relief by LeBlanc *et al*. [16] which was 11 weeks in the one-injection group. However, in our study, the median duration of pain-free period was 32 days. This is caused by reduced survival of patients with advanced HCC which in our study had median survival of 36 days with a range of 15–117 days. This indicates that from the time of EUS injection and response (1–2 weeks) and until death, patients had consistent pain relief (Table 8).

This indicates that EUS-CPN has very low risk of complications, which is the same as reported by several studies [15,23–25].

Conclusion

EUS-CPN appears to be effective and a safe way of palliative pain management in patients with advanced HCC. It should be a potential choice in patients with moderate to severe abdominal pain, as they are not considered for therapeutic intervention. Further evaluation of larger groups of patients in multicenter studies is required to evaluate the optimal technique used.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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