Additive value of dexmedetomidine in endoscopic ultrasound-guided celiac plexus neurolysis for the treatment of liver cancer pain

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Background
Hepatocellular carcinoma is the most common primary liver cancer that usually develops in a background of cirrhosis. It is usually diagnosed at advanced stages and abdominal pain may be the first presentation where it represents a significant cause of morbidity. Celiac plexus neurolysis (CPN) demonstrated good results in the relief of pain as a result of upper abdominal malignancy. Dexmedetomidine is an α2 adrenoreceptor highly selective agonist approved for procedural sedation use.
Patients and methods
Fifty patients who were divided into two groups with hepatocellular carcinoma-associated abdominal pain in need of opioid analgesics underwent endoscopic ultrasound-guided CPN using bupivacaine 0.5% alone with alcohol for the first group and bupivacaine 0.5% plus dexmedetomidine in the second one. Patients give their abdominal pain a score according to the numeric rating scale-11 before, 2, 4, 6, 8, 12, 16, and 24 week after the procedure.
Results
The study have included 50 patients who were divided in two groups: 32 men and 18 women with a mean age of 60.12±5.07 years for group 1 and 58.32±5.03 years for group 2. There were no significant difference between the two groups as regards medical, laboratory, or tumor characteristics. The median pain score decreases from 8.32±0.75 before the procedure to 3.75±3.72 24 week after the procedure in group 1 and from 8.08±0.86 before to 1.67±2.3 24 week after the procedure in group 2. However, there was no significant difference between the two groups in the median pain score during the first 4 weeks of follow-up. There was no statistically significant difference between the two groups as regards the median survival time.
Conclusion
The addition of dexmedetomidine to bupivacaine 0.5% in endoscopic ultrasound-CPN demonstrated beneficial effects as regards the degree and duration of pain relief with negligible effect on patient survival.

Keywords:
celiac plexus neurolysis, dexmedetomidine, hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. The annual number of diagnosed HCC cases is more than one million worldwide. It represents the fifth most common cancer worldwide and the third leading cause of cancer-related deaths [1]. HCC is the end result of some chronic viral infections such as the hepatitis C virus (HCV) or hepatitis B virus [2].

It is generally accepted that most of HCC cases develop in a progressive pattern from acute viral hepatitis passing through various stages of chronic hepatitis to cirrhosis and then HCC [3]. HCC escapes early detection as it progresses silently in patients with a compensated liver function. Diagnosis of HCC usually occurs at advanced stages in developing countries due to limited surveillance resources [4].

Treatment of HCC-associated pain varies according to its cause. Symptomatic treatment with NSAID should be avoided, due to the possibility of hepatotoxicity, gastrointestinal bleeding, and hepatorenal syndrome [5].

Acetaminophen is the agent used as first line in long-term use, while opioids should be reserved as second-line treatment. Liver plays a role in the degradation and

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biotransformation of opioids to their active metabolites, so awareness of their pharmacokinetics is crucial. As they are least affected by renal dysfunction, hydromorphone and fentanyl are usually preferred [5].

Endoscopic ultrasound (EUS)-guided celiac plexus neurolysis (CPN) is the chemical destruction of celiac ganglia and associated neural pathways through injection of dehydrated alcohol into the network of the celiac plexus. This leads to moderate degeneration of the neurons associated with residual fibrosis [6].

Pain exacerbation after EUS-CPN initially was noticed in about 29–34% of cases [7]. To improve the technique, many attempts were done where Sakamoto *et al.* [8] used broad plexus neurolysis near the superior mesenteric artery aiming at administration of the neurolytic agent to a larger number of ganglia.

Dexmedetomidine is an α2 adrenoreceptor highly selective agonist that induces sedation through the activation of adrenoceptors located in the locus coeruleus [9]. The use of dexmedetomidine in a wide range of patients and clinical situations has been approved in the medical literature, including perioperative use [10], procedural sedation [11], and use in children [12]. Alternative routes of administration, including intranasal [13], subcutaneous [14], buccal [15], and intrathecal [16] routes have also been reported. Owing to the observation that patients sedated with dexmedetomidine remain more arousable than patients sedated with benzodiazepines, using dexmedetomidine to provide anxiolysis, sedation, and analgesia for patients with severe symptoms near the end of life has been of clinical interest. Subsedating doses of dexmedetomidine have been used as an analgesic; however, there are no controlled clinical trials investigating this specific use [17].

We tried to evaluate the additive value, efficacy, and safety of adding dexmedetomidine to bupivacaine and alcohol on pain relief in EUS-CPN for HCC-associated pain.

Patients and methods

Study design

This is a prospective, observational, case–control study that was conducted on patients attending the Hepatology and Early Detection of HCC Outpatient clinics or patients admitted to the Hepatology and Gastroenterology Unit, Specialized Medical Hospital, Mansoura University, Egypt.

Patients

The study enrolled 50 patients diagnosed with HCC complaining of moderate-to-severe abdominal pain in need of opioid analgesics and patients who are not candidate for tumor-directed therapies. We excluded patients with uncorrectable significant coagulopathy, conditions altering upper gastrointestinal tract anatomy, for example, gastric bypass making endoscopic access not possible, history of psychiatric disturbance, or history of hepatic encephalopathy. Each patient was exposed to full medical history and clinical assessment.

The patients were divided into two groups:

Group 1: EUS-guided CPN was done using bupivacaine 0.5% and then alcohol (95%).
Group 2: EUS-guided CPN was done using bupivacaine 0.5% plus dexmedetomidine 200 mg and then alcohol (95%).

Laboratory assessment

Baseline complete blood count, liver function tests, α-fetoprotein, and renal functions were done to assess the liver function state by Child–Turcotte–Pugh classification to evaluate the outcome of liver cirrhosis.

Imaging studies

Baseline tumor characteristics including site, number of focal lesions, maximum tumor diameter, and presence of portal vein thrombosis were collected from imaging reports done at the Specialized Medical Hospital.

Pain assessment

Patients give their pain a score from 0 to 10 according to the numeric rating scale-11 before and 2, 4, 6, 8, 12, and 16 week after the procedure and then every month till 6 months or death of the patient to detect the patient.

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, a 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 assuring that there is no backflow of blood and then 3 ml bupivacaine 0.5% was injected in the first group and bupivacaine 0.5% plus dexmedetomidine 200 mg in the second group. After that, 15–20 ml of alcohol (95%) was injected using another syringe. With the injection of alcohol, an echogenic shadow was visualized on EUS around the area of the injection.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (SPSS Inc, Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using mean, SD for parametric data and median, minimum and maximum for nonparametric data after testing normality using the Shapiro–Wilk test. Significance of the obtained results was judged at the 0.05 level and all tests were two tailed. Student's *t*-test and Mann–Whitney *U*-test were used to compare between the two studied groups with parametric and nonparametric variables, respectively. χ^2-Test and Fischer's exact test were used to compare categorical variables as appropriate, Kaplan–Meier survival curve, and log-rank test were used to compare the effect of drug regimen use on survival time.

Ethics

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

Results

Patient and tumor characteristics

The study have included 50 patients who divided into two groups: 32 men and 18 women with a mean age of 60.12±5.07 years for group 1 and 58.32±5.03 years for group 2. Table 2 showed the medical history and

Table 1 Demographic characteristics of the studied groups

	Group 1 (*N*=25)	Group 2 (*N*=25)	Test of significance
Age (mean±SD) (years)	60.12±5.07	58.32±5.03	t=1.26P=0.21
Sex [*N* (%)]			
Male	15 (60.0)	17 (68.0)	χ^2=0.35P=0.56
Female	10 (40.0)	8 (32.0)	

Table 2 Medical history and clinical examination of the studied groups

	Group 1 (*N*=25)	Group 2 (*N*=25)	Test of significance
DM	10 (40.0)	7 (28.0)	χ^2=0.80P=0.37
Hypertension	8 (32.0)	4 (16.0)	χ^2=1.75P=0.19
Liver			
Bilharziasis	3 (12.0)	1 (4.0)	FETP=0.61
HCV	22 (88.0)	24 (96.0)	
Hepatic focal lesions			
Left lobe	5 (20.0)	0	χ^2=5.56P=0.062
Right lobe	8 (32.0)	10 (40.0)	
Multifocal	12 (48.0)	15 (60.0)	
Portal vein			
Patent and dilated	23 (92.0)	19 (76.0)	χ^2=2.38P=0.12
Portal vein thrombosis	2 (8.0)	6 (24.0)	
Spleen			
Absent	3 (12.0)	2 (8.0)	MCP=0.14
Mild	7 (28.0)	4 (16.0)	
Moderate	13 (52.0)	18 (72.0)	
Marked	2 (8.0)	1 (4.0)	
Ascites			
Negative	23 (92.0)	19 (76.0)	χ^2=2.38P=0.12
Positive	2 (8.0)	6 (24.0)	
Lymph node involvement			
Negative	22 (88.0)	23 (92.0)	FETP=1.0
Positive	3 (12.0)	2 (8.0)	

clinical examination of the two groups: those with diabetes melitus (DM) and hypertension were 40.0 and 32.0%, respectively, in group 1 and in 28.0 and 16.0% of group 2, respectively. The underlying etiology of liver cirrhosis was similar in the two groups and includes HCV and bilharziasis. There was no significant difference between the two groups as regards tumor characteristics including site, number of focal lesions, and degree of splenomegaly, presence of ascites, portal vein thrombosis, or lymph node involvement. Table 3 summarizes the laboratory characteristics of the studied groups.

Table 3 Laboratory results of the studied groups

	Group 1 (*N*=25)	Group 2 (*N*=25)	Test of significance
Albumin (g/dl)	3.26±0.57	3.25±0.67	t=0.05P=0.96
Bilirubin (mg/dl)	1.46±0.72	1.41±0.59	t=0.26P=0.80
WBCS	4.89±2.05	4.54±1.66	t=0.66P=0.51
Hemoglobin (g/dl)	11.33±1.79	10.82±1.55	t=1.08P=0.28
Platelet	102.48 ±45.94	108.36 ±52.56	t=0.42P=0.68
INR	1.33±0.17	1.38±0.21	t=0.86P=0.39
AFP (ng/dl)	92 (3.9–2000)	85 (11–241)	z=1.47P=0.14
ALT (U/l)	35 (20–182)	38 (22–182)	z=0.30P=0.76
AST (U/l)	69 (32–203)	68 (32–203)	z=0.26P=0.79

All parameters described as mean and SD except AFP, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) described as median (minimum–maximum).

Outcomes of the procedure

Table 4 shows the median pain score change before the procedure and during the follow-up period. The median pain score decreases from 8.32±0.75 before the procedure to 3.75±3.72 24 weeks after the procedure in group 1. In group 2, the median pain score decreases from 8.08±0.86 before to 1.67±2.3 24 weeks after the procedure. However, there was no significant difference between the two groups in the median pain score during the first 4 weeks of follow-up as shown in Fig. 1.

Patient survival

During the period of follow-up that reached more than 1 year in some patients, only one patient (4.0% of cases) of group 2 died before 1 year in comparison to five patients (20.0% of cases) in group 1 (Table 5). Table 6 shows the median survival time of the two groups that was 7 months for group 1 and 12 months for group 2; however, there was no statistically significant diference between the two groups.

Discussion

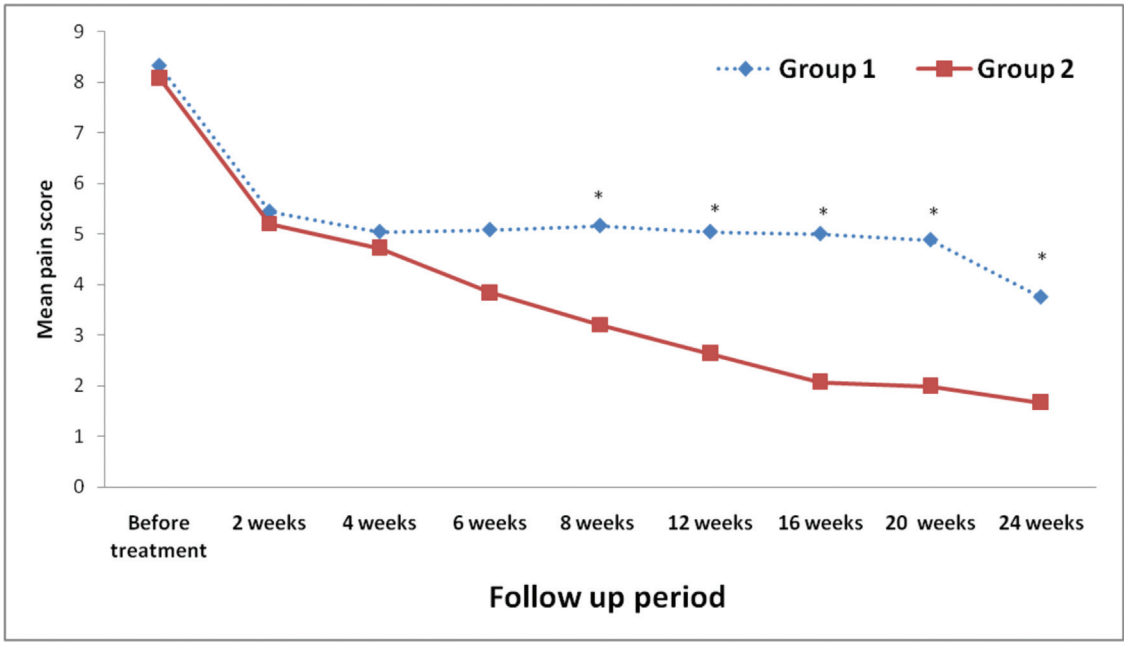
It is broadly accepted today that HCC represents an aggressive type of tumor as it mostly develops in a background of chronic liver disease, chiefly liver cirrhosis. In developing countries like Egypt, liver cirrhosis due to chronic HCV infection is the main precancerous lesion. The limited surveillance resources

Table 4 Comparison of mean pain score between the studied groups and percent of change during follow-up period

Pain score	Group 1 (*N*=25)	Group 2 (*N*=25)	Test of significance	% of change from before treatment for group 1	% of change from before treatment for group 2
Before treatment	8.32±0.75$^{A,B,C,D,E,\#,\dagger,\$}$	8.08±0.86$^{A,B,C,D,E,\#,\dagger,\$}$	t=1.05P=0.29		
2 weeks after treatment	5.44±1.16^{A}	5.20±0.9^{A}	t=0.81P=0.42	34.62	35.6
4 weeks after treatment	5.04±1.09^{B}	4.72±0.68^{B}	t=1.24P=0.22	39.4	35.6
6 weeks after treatment	5.08±1.61^{C}	3.84±1.37^{C}	t=2.93P=0.005*	39.42	52.5
8 weeks after treatment	5.16±1.97^{D}	3.2±1.5^{D}	t=3.95P<0.001*	37.9	60.4
12 weeks after treatment	5.04±2.9^{E}	2.64±2.4^{E}	t=3.22P=0.002*	34.6	67.3
16 weeks after treatment	5.0±3.6$^{\#}$	2.08±2.95$^{\#}$	t=3.14P=0.003*	39.9	74.3
20 weeks after treatment	4.88±3.8†	2.0±3.1†	t=2.94P=0.005*	41.3	75.2
24 weeks after treatment	3.75±3.72$^{\$}$	1.67±2.3$^{\$}$	t=2.26P=0.029*	54.9	79.3
Repeated measures analysis of variance	F=11.64P=0.003*	F=75.41P<0.001*			

Similar superscripted letters between groups denote significant difference between groups. All parameters described as mean and SD.
*P<0.05, statistically significant.

Figure 1



Line graph showing the mean pain score change between the studied groups.

Table 5 Comparison of survival between the studied groups

	Group 1 (*N*=25)	Group 2 (*N*=25)	Test of significance
Survived	20 (80.0)	24 (96.0)	χ^2=3.03
Died	5 (20.0)	1 (4.0)	*P*=0.083

Table 6 Comparison of median survival time between the studied groups

	Group 1 (*N*=25)	Group 2 (*N*=25)	Test of significance
Survival [median (minimum–maximum)] (time/months)	7.0 (5.0–12.0)	12.0 (5.0–12.0)	Log-rank χ^2*P*=0.083

as well as the low socioeconomic and cultural standards of patients in Egypt make the diagnosis of HCC at early stages very difficult.

In HCC, pain usually occurs in advanced stages which may be related to the disease or therapies done to the patient and represents a significant cause of morbidity. Medications used to manage pain associated with HCC like NSAIDs or opioid analgesics face many obstacles as the liver plays an important role in biotransformation and catabolism of opioids which already is cirrhotic or the drugs are contraindicated as NSAIDs.

CPN has been used as an alternative treatment for managing cancer-associated pain on a wide range. In the past years, CPN had been done percutaneously or during open surgery. Anterior or posterior percutaneous CPN may be done guided by abdominal ultrasound, fluoroscopy, or computed tomography and recently EUS-guided [18]. National Comprehensive Cancer Network guidelines recommend EUS-CPN for the management of severe pain associated with cancer [19].

Sakamoto *et al.* [8] recently described a variation of EUS-guided neurolysis that is the EUS-guided broad plexus neurolysis (EUS-BPN). In EUS-BPN, a neurolytic agent is injected around the origin of the superior mesenteric artery to produce a more wide distribution of the neurolytic agent. To achieve long-lasting pain alleviation, neurolytic agents, and the used delivery methods may need improvement.

Our study has included 50 patients, 32 men and 18 women (men : women ratio is 1.78 : 1) with a mean age of 60.12±5.07 years for group 1 and 58.32±5.03 years for group 2 (Table 1). This seems logic as we deal with patients with cancer where it is broadly accepted that male gender and elder age are well-known risk factors for nearly all tumors.There was no statistically significant difference between the groups as regards clinical, laboratory, or tumor characteristics such as number, site of focal lesions, presence or absence of ascites, portal vein thrombosis, or lymph node affection (Tables 2 and 3). This is very important because the two groups must be cross-matched to avoid the effects of patient characteristics, the pattern, or aggresiveness of the tumor on the patient response.

The mean pain score of group 1 was 8.32±0.75 before the procedure that decreased during the period of follow-up to 3.75±3.72 24 weeks after the procedure with 54.9% improvement in pain alleviation. On the other hand, in group 2 the mean pain score was 8.08 ±0.86 before the procedure and decreased significantly to 1.67±2.3 24 week after the procedure with 79.3% improvement in pain alleviation (Table 4). This go hand in hand with two subsequent meta-analyses that showed a 72–80% mean rate of pain alleviation with a much lower rate of complete pain response [20,21]. Another two meta-analyses evaluated the utility of EUS-CPN in unresectable abdominal cancer-associated pain and showed an alleviation rate of 73–80% with 1–2 months treatment duration approximately [22,23].

In this study, only two cases achieved complete pain relief with no need to analgesics which was statistically insignificant. This is similar to the finding of Levy *et al.* [20] who showed that many patients who underwent the EUS-CPN for intra-abdominal cancer-associated pain still required the same doses of analgesic. However, they recommend EUS-CPN as an adjunct method to standard pain treatment. The residual post-neurolysis pain may be related to nonvisceral pain, due to the tumoral invasion to the muscles or surrounding connective tissue and factors related to the technique used such as timing of the procedure, type of technique, or quantity of alcohol injected have not been extensively studied.

In this study, there was no statistically significant difference between the two groups as regards the degree of pain alleviation till the first 4 weeks after the procedure. The difference between the two groups started from the fourth week and continued till the period of follow-up at 6, 8, 12, 16, 20, and 24 weeks with *P* equal to 0.005, less than 0.001, 0.002, 0.003, 0.005, and 0.029, respectively (Table 4 and Fig. 1). This suggests that a good sustained pain relief achieved in group 2 may be related to the addition of dexmedetomidine.

The mechanisms of the analgesic actions of α2 agonists have not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the central nervous system. Drugs may act at any of these sites to reduce nociceptive transmission, leading to analgesia. Another physiologic prominent action of α2 adrenoceptors is their reduction of calcium conductance into cells, thus inhibiting neurotransmitter release [24].

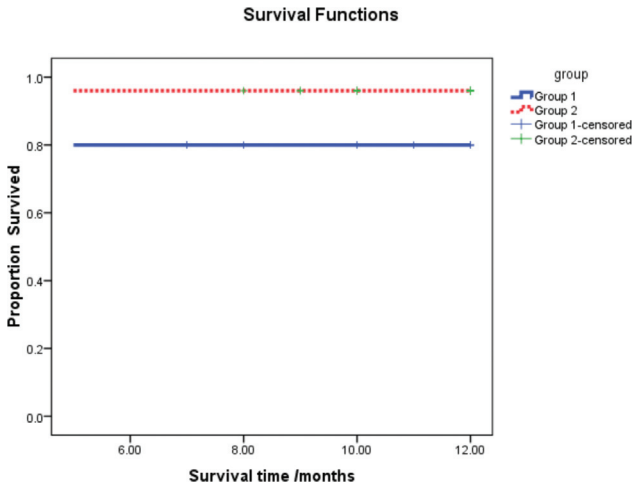
This technique has been used in few studies only. One randomized, controlled trial compared direct celiac ganglia neurolysis with central neurolysis and showed positive response rate at the seventh day and complete response rates were higher in the group of celiac ganglia neurolysis [25].

Parallel to our results, Sakamoto *et al.* [8] compared the safety and efficacy of EUS-CPN and EUS-BPN in patients with pain related to pancreatic cancer. They found that EUS-BPN was more effective; especially in cases of extensive spread of tumor within the peritoneal cavity beyond the celiac plexus distribution and that the procedure did not lead to serious complications.

On the other hand, there was no significant difference between the groups as regards the patient survival after the procedure. In group 1, 20 patients (80.0% of cases) survived and five patients (20.0% of cases) died before the duration of follow-up with a median survival time of 7.0 months. In group 2, 24 patients (96.0% of cases) survived and one patient (4.0% of cases) died with a median survival time of 12.0 months (Tables 5 and 6 and Fig. 2). From these data, it appears that there is improvement in the survival of patients in group 2 although it does not reach a statistical significance.

Improvements in pain alleviation, either intensity or duration, are associated with improvement in quality of life such as the ability to work, sleep, and pleasuring events and not necessary improvement in patient survival as it depends on the reserve functions of the liver and aggressiveness of the tumor.

Figure 2



Kaplan–Meier curve for survival comparison between the studied groups.

Our study has some limitations such as the relative small number of patients included in our study, the relatively narrow scope of our patients as we took patients with liver cancer only not upper abdominal malignancy, lack of reporting side effects and lastly we have not compared between the bilateral and central techniques of EUS-CPN as the technique may affect the delivery of the drug to the neuronal axons, thereby affecting the patient response. In spite of this, a study done by LeBlanc *et al*. [26] showed no difference between the two techniques; however, good pain alleviation was achieved via the central technique which is easier to perform. To summarize, EUS-CPN appears to be a safe and effective technique for the treatment of pain associated with upper abdomen malignancy. Dexmedetomidine exerted a powerful and durable analgesic effect in EUS-CPN.

Conclusion

EUS-CPN is a safe way of managing pain associated with liver cancer. The addition of dexmedetomidine to bupivacaine 0.5% in EUS-CPN demonstrated beneficial effects as regards the degree and duration of pain relief with negligible effect on the patient survival. Further larger-scale multicenter studies are needed to assess the safety of the used drug.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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