Randomized Controlled Trial

Dexmedetomidine in Fluoroscopic Guided Splanchnic Nerve Neurolysis for Pain Control: A Randomized, Controlled Trial

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Background: Splanchnic nerve neurolysis (SNN) shows beneficial effects in reducing malignancy-associated refractory abdominal pain. Using adjuvants, such as dexmedetomidine to improve the pain was studied.

Objective: To detect any role of dexmedetomidine as an additive to local anesthetics with an alcohol injection in the chemical SNN process to improve pain in patients having upper-abdominal cancer.

Study Design: Double-blinded, prospective randomized study.

Setting: Department of Anesthesia and Intensive Care, faculty of medicine, Minia University, Egypt.

Methods: Forty patients with upper-abdominal malignancy-associated refractory abdominal pain underwent fluoroscopic guided SNN were divided into 2 groups. The SNN was performed by using 1.5 mL lidocaine 1%, dexmedetomidine 2 µg/kg, and then an injection of 4.5 mL of ethanol 96% on each side in group D and without dexmedetomidine in group C is done. Patients gave the score of abdominal pain expressed by the Visual Analog Scale (VAS), which measures the pain intensity. Scors were recorded prior to injection, during injection, after injection by 5 min, and after 2, 6, 12, 24, 72 hours, one week (W), 2 W, one month (M), and 2 M. Also, we recorded the amount of morphine required to relieve the residual pain after injection, the effect of procedure on quality of life (QOL), and any complication after injection.

Results: VAS scores showed a significant increase in group C in comparison to group D during injection, after injection by 5 min, 2, 6, 12, 24 hours, one and 2 months ($P < 0.0001$, 0.0001, 0.029, 0.031, 0.025, 0.040, 0.020, 0.015), respectively. The morphine requirement was significantly increased at one W, one M, and 2 M in group C in comparison to Group D ($P < 0.044$, 0.017, 0.033) with no significant change in the QOL observed between groups.

Limitations: The limitations of this study were a relatively small sample size and short period of follow-up.

Conclusions: This study revealed that using dexmedetomidine in the chemical SNN process improves the pain results from injection of alcohol and refractory cancer related pain with reduction in the consumption of morphine in patients with upper-abdominal malignancy.

Key words: Splanchnic nerve neurolysis, dexmedetomidine, alcohol, chronic cancer pain

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The most common complaint in patients suffering from upper-abdominal malignancy is severe pain related to the abdomen (1,2). Despite the principles of the World Health Organization's (WHO) 3-step analgesic ladder that recommended analgesics to improve that pain, the higher dose of analgesics still cannot achieve satisfactory analgesia in about 20% of patients at the intermediate and last stages (3).

In addition, such medical management is accompanied by bad quality of life (QOL) due to the many and troubling side effects (4). In some cases, patients may suffer from side effects related to the drug or pain that is hard to treat. These patients may benefit from an early interventional pain technique. Interventional techniques may range from simple nerve blocks to regional or neurolytic blocks, such as celiac plexus and splanchnic nerves (5). Fluoroscopy guided chemical SNN is generally achieved using phenol or alcohol that gives acceptable pain control for about 3 to 6 months (6). Injection of alcohol induces severe transient pain caused by local irritation in about 29–34% of cases, so many attempts were made to improve the neurolysis technique (7).

Traditionally, a nerve block with local anesthetic was given to prevent or decrease pain at the same site of injection, such as lidocaine or ropivacaine, to reduce the acute pain induced by alcohol during the operation (8,9). Several studies demonstrated that adding dexmedetomidine to local anesthetic increases its potency and decreases their required dosage (10). Recently dexmedetomidine was used as a complementary analgesic for the treatment of chronic pain and in particular pain related to cancer (11).

In this study, our group evaluated the additive effect, safety, and efficacy of adding dexmedetomidine to bupivacaine with alcohol in SNN on injection pain and refractory cancer related pain in patients suffering from malignancy in the upper abdomen.

Methods

Study Design

The study was conducted in EL-Minia University Hospital between September 2020 and July 2022 on patients who underwent SNN under fluoroscopic guidance. This study was approved by the ethical committee of EL-Minia University N0 673 8/2020 and registered at clinicaltrials.gov ID: NCT05291364.

Patients

The study included 40 upper abdominal cancer patients of both genders, aged between 25 and 70 years, who suffered from persistent moderate to severe abdominal pain due to their cancer (visual analog scale (VAS) score > 4), which has no response to opioids or complaining from intolerable and annoying side effects of opioid drugs.

Exclusion criteria were patients having bleeding disorders or coagulation abnormality, poor cardiac or poor respiratory function, skin infection or wounds at site of needle insertion, psychiatric diseases, and patients who refused to participate.

Randomization

All patients gave written informed consent after receiving adequate explanation about the study maneuvers and possible risks. The patients and the anesthetist who performed the block were unaware of the study group they had been included in. All patients received a splanchnic nerve block on both sides with 1.5 mL of lidocaine 1% and diluted in 0.9% sterile saline in total volume 7.5 mL followed by an injection of 4.5 mL of ethanol 96% in the same site. The patients were randomly assigned according to the computer-generated random numbers with closed-sealed envelopes into 2 parallel equal groups (20 patients in each group) according to sample size: dexmedetomidine group (group D), dexmedetomidine 2 μg/kg was added to the lidocaine syringe and control (group C) without dexmedetomidine.

Procedure Steps

Patients underwent routine investigations, such as complete blood count, full coagulation profile, renal function tests, liver function tests, and random blood sugar. Each patient fasted 6 hours for food and 2 hours for water and stopped the morphine on the day of the procedure. Alcohol neurolysis was performed in the operating room through collaboration between a radiologist and a pain physician, and all medications and cardiopulmonary resuscitation equipment were available. An intravenous line (cannula 20-gauge) was inserted before the injection; 500 mL of 0.9% sterile saline bottle was given to prevent severe decrease in blood pressure. All patients were sedated with midazolam in a dose of (0.01–0.02 mg/kg) and incrementally doses of propofol in a dose of (0.5–1 mg/kg). Continuous monitoring of the patients was done using noninvasive blood pressure, continuous electrocardiogram, and pulse oximeter for monitoring of oxygen saturation.

The patient was then lying in a prone position with a pillow as a support under the upper part of the abdomen to increase thoracic kyphosis and were supplied with 3 L/min oxygen by a nasal cannula. All procedures were done under complete and strict aseptic environment, with sterilization of patient's back. The skin was anesthetized with 2% lidocaine before introducing the needles. An appropriate spinal-type 22G 150 mm needle would be advanced towards the inferior border of the eleventh intercostal space approximately 6 cm away from midline and advanced until it is in contact with the anterolateral aspect of T11, where the splanchnic nerves typically are positioned. Once the needle is in the appropriate position, we confirmed its location by anterior-posterior view and lateral view using 1–3 mL of nonionic contrast dye, which spread under fluoroscopic guidance.

Aspiration was done using a syringe to confirm that no vessel had been punctured and then lidocaine plus dexmedetomidine was injected in group D and lidocaine was injected in group C on each side. After 3 min, 4.5 mL ethanol 96% was injected on each side with intermittent fluoroscopy to confirm appropriate spread of the solution. After injection, all patients were closely observed for any post-injection complications and discharged home after normal and stable vital signs were noticed and recorded by the medical team or after a total period of 6 hours.

Outcome Measures

Using the VAS (0, which means no pain to 10, which means the worst pain) (12), the patients record the pain level by making a handwritten mark on a 10-cm straight line. The pain scores of the injection (alcohol burning pain) were recorded during injection and 5 minutes after. Also, cancer related pain was recorded before the injection and after at 2, 6, 12, 24, 72 hours, one week, 2 weeks, one month, and 2 months.

The secondary outcomes were the time with hours of rescue analgesic requirement, such as morphine sulphate tablets. Total daily morphine equivalent was recorded. The performance status scale (PS) objectively assessed by the team of the doctors and nursing staffs. The PS score of 0-4 was objectively determined by the medical team (Table 1) (13). The uniscale QOL was the Single-Scale Evaluation reported by patients. The uniscale QOL represents the improvement of performance of lifestyle as somnolence, enhancing of intestinal function with restored appetite, and weight gain (13). The patients recorded their performance by making a mark on a 10-cm analog scale (0 indicating very dissatisfied and 10 indicating very satisfied). Hence, PS and QOL scores were recorded at baseline before the procedure and then after the intervention on the day of procedure (D1), then one week, 2 weeks, one month, and 2 months. The rate of any complications, such as paresthesia, colic, diarrhea, hypotension, back pain, discitis, and pneumothorax, during or after the procedure were recorded.

Table 1. *Performance status*.

1.	No symptoms, normal life.
2.	Able to carry out normal activities, but has returned to part-time or less strenuous employment.
3.	Unable to work, but can care for personal needs.
4.	Limited in care for self. Unable to care for self and comfined to bed.

Statistical Analysis

Data were checked, entered, and analyzed using IBM SPSS software, version 26 for data processing. For categorical variables we used frequencies and percentages, Fisher exact was the test used to compare the 2 groups, followed by the chi-square test. Results were presented as mean ± standard error of mean for normally distributed data and compared using a 2-sample Student's t test. The nonparametric data, presented as median and IQR and Mann-Whitney U-tests, were calculated to compare the medians of 2 independent groups. The paired t-test was used for parametric data and the Wilcoxon signed-rank test was used for nonparametric data to perform pairwise comparisons. Before the study, the number of patients required in each group was determined after a power calculation according to data obtained from a pilot study. In that study the mean VAS at 24 hours in group I was 3 ± 0.2 and in group II was 3.6 ± 0.6. A sample size of 20 patients in each group was determined to provide 80% power for independent samples t-test at the level of 0.05 significance, using G*Power 3.1 9.2 software.

Results

Following randomization of 47 patients, 3 patients (2 from Group D and one from Group C) were excluded due to failure of the block. Two patients in each group either died or were lost to follow-up and excluded. So, the study included 40 patients (Fig. 1).

All the patients were on high dose morphine therapy at the time of the splanchnic nerves neurolysis (SNN) and continued to use it. Patient characteristics

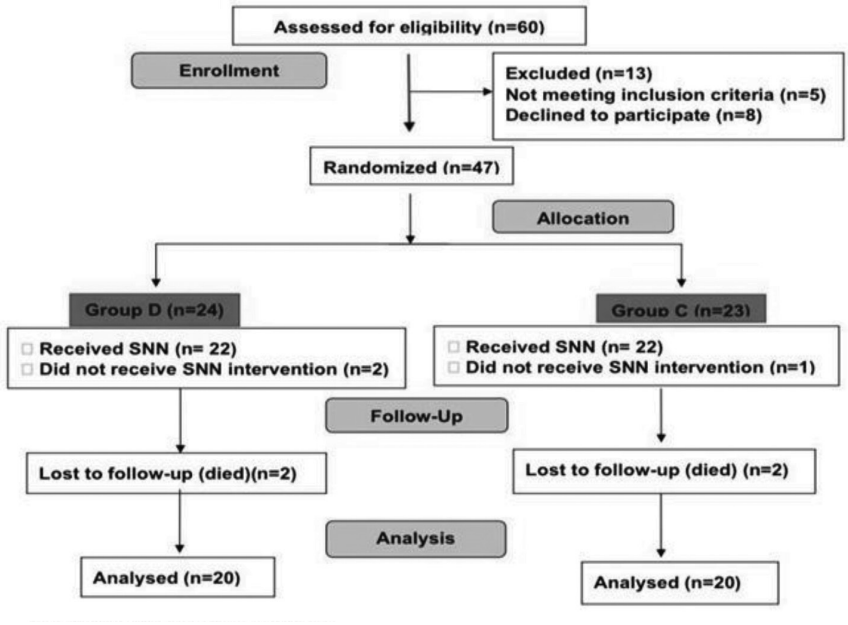

Fig. 1. *CONSORT flow diagram for patients.*

were the same between the 2 groups (Table 2). The VAS score of burning pain during and 5 minutes after the injection were increased in group C when compared with group D ($P < 0.0001$) (Table 3). Compared with the preoperative VAS score in both groups, the postoperative VAS score for cancer related pain decreased significantly (Table 4), which started to decline after 2 hours and was maintained at 2 months follow-up. VAS scores differ between the 2 groups, there was a significant decrease in group D compared to group C on the first 24 hours, after one and 2 months (Table 4).

The first analgesic requirement was decreased significantly after 15.95 ± 4.51 hours in group D while in group C was after 6.70 ± 2.69 hours ($P < 0.0001$). The daily morphine requirements after injection at one week, 2 week, one month, 2 months, decreased significantly after SNN in both groups ($P < 0.0001$), but group D represent a more satisfying result than group C at one week, one month, and 2 months ($P < 0.04$, 0.017, 0.033), respectively (Table 5).

The patient satisfaction (PS and QOL) scores changed after SNN showed significant improvement in both groups with no significant difference between them (Table 6). There were no serious complications in either group with no significant difference between them (Fig. 2).

Discussion

Alcohol contacts the nerves directly during the process of neurolysis and by inducing dehydration, cholesterol, phospholipids, and cerebrosides are extracted out from neuronal cells. In addition, mucoproteins are markedly precipitated which leads to sclerosis of the nerve fiber and also myelin sheath; consequently destroy, block the nerve, and induce pain relief (14). Despite its benefits to control the refractory pain, these neurolytic agents stimulate tissues too potently which may lead to immediate intense burning dysesthesias. This pain may occur during the injection or just afterwards, secondary to chemical neuritis which affects the satisfaction and cooperation of patients during the procedure (8,15). Additionally, its full effect appears in a 3 to 5 days period (16). Therefore, we used additives to the routine local anesthetic and alcohol to improve the quality of pain relief.

Previous studies (1,17-19) have demonstrated the technique and efficacy of fluoroscopic guided alcohol neurolysis in patients who complain of annoying abdominal pain that is unresponsive to pain killers and other drugs. However, to our knowledge, few studies have described the benefits of using an additive to alcohol as an attempt for pain improvement.

This trial included 40 patients divided into 2 study groups, dexmedetomidine group D and control group C. We revealed that adding dexmedetomidine to local anesthetic could reduce burning pain during injection more effectively than alcohol and local anesthetic alone, the pain was significantly reduced in group D during injection and 5 minutes after it. The burning pain induced by an injection of alcohol can be partially avoided with an injection of local anesthetics before alcohol at the same site (20). However, this method still induces severe pain during the procedure, expressed by the increased VAS score in group C. The authors explained this deterioration does not mean inadequate

Table 2. *Patient characteristics*.

Variable	Group D n = 20	Group C n = 20	*P* value
Age/year (mean ± SD)	56.55 ± 12.22	55.65 ± 13.02	0.827
Gender (n %) Female Male	 7 (35) 13 (65)	 8 (40) 12 (60)	 0.744
Weight (kg) (mean ± SD)	70.15 ± 7.30	67.15 ± 5.56	0.453
Height (cm) (mean±SD)	166.50 ± 8.72	162.55 ± 8.33	0.623
Cancer Type (n %) Pancreatic Hepatic or gallbladder Gastric	 15 (75) 3 (15) 2 (10)	 16 (80) 2 (10) 2 (10)	 0.70 0.63 1.0
Cancer Status Active Remission	 19 (95) 1 (5)	 18 (90) 2 (10)	 0.54
Duration of procedure (min) (mean ± SD)	18.70 ± 1.89	19.100 ± 1.88	0.508

D group (dexmedetomidine), C group (control), Values are presented as mean ± SD by t test, or number and percentage (n %) by Pearson chi-square.

Table 3. *Visual analog scale (VAS) score of pain during injection among the 2 groups*.

Variable	Group D n = 20	Group C n = 20	*P* value
During injection	5 (1)	8 (2)	0.0001#
5 min after injection	4 (1)	6 (2)	0.0001#

D group (dexmedetomidine), C group (control). Values are presented as median IQR.
#: Significant difference between groups at *P* value < 0.05 by Mann-Whitney U test.

anesthesia, but may be due to the concentrations of alcohol and local anesthetic that is diluted when injected at the same site, which reduced the analgesic effect of local anesthetic (9).

Several studies (21-23) have documented that adding dexmedetomidine to a local anesthetic can improve the postoperative pain control (shorter onset time and longer duration). Kang et al (9) described that the patients had severe pain with alcohol injection (VAS: 7.73 ± 1.75) when they get injected with alcohol at the same side as the local anesthetic alone, which is close to our results; the median VAS score was 8 (2) in group C, while group D shows a significant decrease in VAS score, which was 5 (1).

The patients in this study, who complained of refractory abdominal pain with initial VAS values as high as the median, was 9 (1.75) in group D, while in group

Table 4. *Visual analog scale (VAS) score of cancer related pain among the 2 groups*.

Variable	Group D n = 20	Group C n = 20	*P* value
Baseline	9 (1.75)	9 (1)	0.932
(H2)	3 (2) *	3.5 (1) *	0.029#
(H6)	3 (1) *	3 (1) *	0.031#
(H12)	3 (0.75) *	4 (1) *	0.025#
(H24)	3 (1) *	4 (1) *	0.040#
(H72)	3 (0.75) *	3.5 (1) *	0.071
(W1)	3 (0.75) *	3 (1) *	0.119
(W2)	3. (1) *	3 (1) *	0.099
(M1)	3 (0) *	3 (1) *	0.020#
(M2)	3 (0) *	4 (1) *	0.015#

D group (dexmedetomidine), C group (control). After 6h (H6), after 12h (H12), after 24h (H24), after 72h (H72), after one week (W1), after 2 weeks (W2), after one month (M1) and after 2 months (M2). Values are presented as median IQR. #: Significant difference between groups at *P* value < 0.05 by Mann-Whitney U test. *: Significant difference within each group when compared with baseline value at *P* value < 0.05 by Wilcoxon signed rank test.

Table 5. *Morphine requirement (mg/d) among the 2 groups*.

Variable	Group D n = 20	Group C n = 20	*P* value*
(Before injection)	111.50±15.98	105.50 ±14.31	0.219
(W1)	37.00±10.39*	47.50±17.43*	0.044#
(W2)	34.00±13.53*	42.53±15.51*	0.073
(M1)	39.00±5.52*	48.00 ±11.72*	0.017#
(M2)	44.00±11.87*	53.00 ±13.80*	0.033#

D group (dexmedetomidine), C group (control). After one week (W1), after 2 weeks (W2), after one month (M1), and after 2 months (M2). Values are presented as mean ± SD by t test. #: Significant difference between groups at *P* value < 0.05 by independent t test. *: Significant difference within each group when compared with before injection at *P* value < 0.05 by paired t test.

C was 9 (1), successfully achieved a significant decline in pain scores immediately after 2 hours and during the follow-up period as told by patients. This goes hand in hand with a systematic review and meta-analysis done by Matsumoto and his college (24) proving that percutaneous SNN was safe and very effective in the treatment of refractory pain associated with malignancy and reducing the requirement of opioids.

Also parallel to our results, Ozyalcin et al (25) compare the efficacy of celiac plexus compared to SNN

Table 6. *Patient satisfaction among the 2 groups.*

Variable	Group D n = 20	Group C n = 20	*P* value*
PS			
(Before injection)	4(1)	4(1)	0.901
(D1)	3(1) *	3 (1) *	0.799
(W1)	2(0) *	2(1) *	0.173
(W2)	2(0) *	2(0) *	0.637
(M1)	2(0) *	2(0) *	0.681
(M2)	2(0.75) *	2(1) *	0.727
QOL			
(Before injection)	2(0)	2(0)	0.568
(D1)	7(2) *	7(0) *	0.862
(W1)	7(1.75) *	7(0.75) *	0.560
(W2)	7.5(1) *	8(1) *	0.689
(M1)	8(0) *	8(0.75) *	0.826
(M2)	8(1) *	7.5(1) *	0.094

D group (dexmedetomidine), C group (control). After one (D1), after one week (W1), after 2 weeks (W2), after one month (M1), and after 2 months (M2). Values are presented as median IQR. #: Significant difference between groups at *P* value < 0.05 by Mann-Whitney U test. *: Significant difference within each group when compared with before injection at *P* value < 0.05 by Wilcoxon signed rank test.

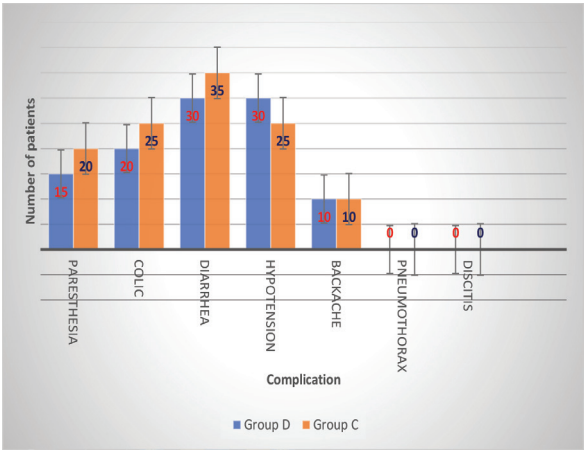

Fig. 2. *Percentage of complications among the 2 groups.*

in cases of pancreatic cancer. They detected that SNN was better than celiac plexus in regard to pain relief, QOL, and analgesic consumption. Comlek et al (26) suggested that splanchnic neurolysis is a durable and effective therapeutic approach for analgesia in pancreatic cancer as the significant change in VAS scores was observed over time ($P < 0.001$). Similarly, Fujita (27) reported that SNN using alcohol decreased upper abdominal cancer pain.

In this study, the dexmedetomidine group patients had significantly lower VAS values at 2 hours, one, and 2 months post injection. There is a limited number of research that using dexmedetomidine along with alcohol injection. Ghafar et al (2) found that the median pain score decreases significantly $P < 0.001$ from 8.32 ± 0.75 before endoscopic ultrasound-Celiac plexus neurolysis to 5.16 ± 1.97 8 weeks after the procedure in group one (used bupivacaine 0.5% alone with alcohol), while in group 2 (bupivacaine 0.5% plus dexmedetomidine), moreover median score of pain decreases from 8.08 ± 0.86 before to 3.2 ± 1.5 8 weeks following the procedure, while no significant difference over the first 4 weeks was observed.

These findings are correspondent to our results as pain scores decreased in group D to 3(0), while group C scores decreased to 4 (1) after 2 months ($P < 0.01$). However, an assessment of pain in Ghafar et al (2) was done after 2 weeks, up to 6 months or death, and they didn't assess the pain score in the first 24 hours. Our group assessed the pain score for chronic cancer pain from the first 24 hours, which revealed a significant reduction in pain scores in group D when compared to group C ($P < 0.05$).

There was a variable time necessary for pain relief after neurolysis with some studies reporting more delayed onset of efficacy and others reporting an immediate pain control (28,29). In this study, pain relief was caried out after 2 hours. Agreeing with previous studies (30,31), the first analgesic requirement in group D was significantly delayed compared to group C ($P < 0.0001$). Hetta et al (30) demonstrated that adding epidural dexmedetomidine to bupivacaine for pain relief in patients undergoing major abdominal cancer surgery reveals excellent pain relief with prolongation of the time of pain control and a lower consumption of morphine. Karmaniolou et al (32) used dexmedetomidine as an adjunct for intravenous regional anesthesia. The study found a shorter time of sensory block onset, longer duration of analgesia intraoperatively, and lower incidence of tourniquet pain in the dexmedetomidine group. Moreover, Memiş et al (31) proved that adding dexmedetomidine to lidocaine improves both the onset and the duration of regional intravenous anesthesia. A meta-analysis by Schnabel et al (33) demonstrated that perineural dexmedetomidine combined with local anesthetics led to a longer period of pain control compared to the sole use of local anesthetics.

According to our analysis, neurolysis was a suitable option and could be significant for people with moderate to severe pain. Furthermore, previous studies (34,35) proved that SNN reduces the amount of opioid

and analgesic intake, our results agree with these results. Although opioids are frequently needed even in patients who underwent neurolysis procedures, our patients felt satisfied and comfort, as indicated by the decreased opioid need which was more relevant with dexmedetomidine in the first week, after one and 2 months.

Improvements in pain control, either duration or intensity, are associated with improvement in QOL, such as the ability to sleep, work, and sharing events (36). QOL was also significantly improved in our groups during the follow-up period as stated by patients. In agreement with Crippa et al (37) prove that early interventional medical and surgical treatment of pain in patients with pancreatic cancer can improve the QOL better than late intervention.

Although the addition of dexmedetomidine resulted in a significant reduction in VAS scores, the PS and QOL values were close between the groups. This may be due to cancer associated with other medical effects, such as metastasis. Few complications may occur with SNN, such as diarrhea, hypotension, chemical peritonitis hematoma, pneumothorax, and neurolysis (38). In our study, no patients had a serious complication and that was in line with Shwita et al (1) study, in which the incidences of diarrhea and orthostatic hypotension were 30% and 34% in SNN group. Similarly, Koyyalagunta et al (19), who used chemical neurolysis for SNN, documented that only 2 patients had symptomatic hypotension, which is treated with an infusion of fluids intravenously. Ahmed et al (39) found that the incidence of hypotension and diarrhea increased after neurolysis, which was 19% and 14%, respectively. Ozyalcin et al (25) supports the use of SNN to control pain in patients with pancreatic cancer, mostly due to a higher analgesic effect and less complications.

Limitations

There are several limitations to our study including the relatively small sample size, so a larger sample size may be required to support the findings; our study had a brief follow-up period of only 2 months long, which is a relatively short period to identify other benefits, disadvantages, and survival rates. Finally, the dose of lidocaine (1.5 mL) used in group C was very small, mainly because our goal was to investigate the effect of dexmedetomidine on pain relief. However, based on our results, another study could be carried out comparing the effect of dexmedetomidine to lidocaine in relieving injection pain.

Conclusion

In conclusion, the present study demonstrates that SNN offers an effective pain relief and alleviates morphine consumption among individuals with upper abdominal cancer. Adding dexmedetomidine to lidocaine with SNN has beneficial effects on reducing pain during injection, degree, and onset of cancer related pain relief. Further randomized studies with larger sample sizes, and with longer follow-up durations, should be done to assess and confirm the safety of the used drug and confirm our findings.

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