Case Series

Prophylactic Perioperative Fluid Infusion Strategy During Splanchnic Nerve Neurolysis to Prevent Systemic Hypotension: A Case Series of 70 Patients With Cancer

Tetsumi Sato, MD, PhD[1,2], Yuichiro Nishibori, MD[2,3], Motoki Sekikawa, MD[2,3], Ryoken Nara, MD[2,4], Tetsu Sato, PharmD[4,5], Yoshiko Kamo, PharmD[4,5], and Rei Tanaka, PharmD[6]

From: [1]Division of Palliative Medicine, Shizuoka Cancer Center, Nagaizumi-cho, Japan; [2]Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Japan; [3]Division of Gynaecology, Shizuoka Cancer Center, Nagaizumi-cho, Japan; [4]Department of Pharmacy, Shizuoka Cancer Center, Nagaizumi-cho, Japan; [5]Department of Pharmacy, Shizuoka Cancer Center, Nagaizumi-cho, Japan; [6]Faculty of Pharmaceutical Sciences, Shonan University of Medical Sciences, Yokohama, Japan

Address Correspondence:
Tetsumi Sato ,MD, PhD
Division of Palliative Medicine
Shizuoka Cancer Center
1007 Shimonagakubo,
Nagaizumi-cho, Sunto-gun,
Shizuoka, 411-8777 Japan
E-mail: te.sato@scchr.jp

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Background: When performing splanchnic nerve neurolysis (SNN), systemic hypotension may occur due to upper abdominal sympathetic blockade; therefore, appropriate periprocedural fluid resuscitation is crucial.

Objectives: The aims of this retrospective observational study were: 1) to validate the efficacy and safety of our prophylactic periprocedural fluid resuscitation in order to prevent systemic hypotension post-SNN, and 2) to explore the indicators that predict the need for additional fluid administration post-SNN.

Study Design: This was a retrospective observational study using medical records from electronic medical charts.

Setting: All patients who received SNN in the Division of Palliative Medicine of Shizuoka Cancer Center from April 2016 through November 2022 in order to relieve pain caused by upper abdominal cancer and/or abdominal paraaortic lymph node swelling, had their electronic medical charts reviewed. Pancreatic cancer (n = 41) was the primary pain origin.

Methods: SNN was performed with the patient prone. Under fluoroscopic guidance a transdiscal approach using a 22G nerve block needle was utilized. The patients maintained their prone position for an hour postprocedure and rested in bed until the following morning. Urine output and blood pressure were measured every postprocedure 4 hours. One thousand mL of dextran 40 solution and 1,000 mL of lactated Ringer's solution were administered as basic fluids during the perioperative 24 hours; additional lactated Ringer's solution was adminstered when oliguria and/or hypotension was observed post block. We recorded patient background data, including the primary malignancy site, clinical classification of pain mechanism, performance status (Eastern Cooperative Oncology Group), presence of diabetes mellitus, hypertension, serum albumin level, hemoglobin level, hematocrit level, C-reactive protein level, estimated glomerular filtration rate, glomerular filtration ratio, presence of celiac plexus invasion and/or peritoneal dissemination, neurolytic agent dose, postblock pyrexia, and survival time post-SNN.

Results: Seventy cases (68 patients, 62.5 ± 12.0 years, 32 men and 36 women, duplicated in 2) were analyzed. The volume of anhydrous ethanol administered as the neurolytic agent was 16.8 ± 2.6 mL. Fourteen patients (21%) received 250 – 1,250 mL of lactated Ringer's solution as additional postprocedure fluid due to oliguria. No systemic hypotension was observed at pre- or postprocedure. No clinical signs of excessive fluid, such as pleural effusion, ascites, edema, and/or dyspnea, was observed. The only indicator to predict the need for additional fluid administration was the dose of neurolytic agent (anhydrous ethanol).

Limitations: The limitations of this study include, firstly, its single-center retrospective observational design. Secondly, although the number of patients in this study was relatively large for a single-center clinical report of SNN, it would probably be more effective to have additional cases in a future prospective study, which would contribute to establishing a more precise method

of fluid resuscitation in order to avoid systemic hypotension induced by SNN.

Conclusion: Our prophylactic perioperative fluid resuscitation for treating systemic hypotension post-SNN is sufficient and safe.

Key words: Splanchnic nerve neurolysis, sympathetic blockade, adverse event, hypotension, fluid resuscitation

Ethics: This clinical study was approved by the Institutional Review Board for Clinical Researches Studies at the Shizuoka Cancer Center (#J2023-57-2023-1-3).

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Splanchnic nerve neurolysis (SNN), which is effective for upper abdominal visceral pain and/or sympathetic pain associated with enlarged paraaortic lymph nodes entering the spinal cord via the celiac plexus and splanchnic nerves, is beneficial for patients who are refractory to pharmacotherapy (1-10). SNN is indicated not only for opioid-tolerant patients, but also for patients at the early stages of the disease who take low opiod doses; SNN is also indicated for opioid-naïve patients.

SNN via a transdiscal approach in the retrocrural space, as well as a paravertebral approach, are effective, safe, and relatively easy procedures with fewer complications when compared to traditional celiac plexus neurolysis (6-10). However, since SNN is a sympathetic nerve block with a rather broad area of control, one of the most important points to keep in mind when performing it is that the procedure may cause systemic hypotension. This hypotension is a result of arterial vasodilatation in the upper abdominal viscera. Although the incidence of this complication has been reported in around a quarter of patients (6,8), fluid resuscitation methods have not been established. The primary purpose of our retrospective observational study was to verify the validity and safety of using a periprocedural fluid resuscitation strategy during SNN. The secondary purpose was to identify risk factors for systemic hypotension induced by SNN.

Study Design

This was a retrospective observational study using medical records from electronic medical charts.

Setting

All patients who received splanchnic nerve neurolysis in our department from April 2016 through November 2022 to relieve pain caused by upper abdominal cancer and/or abdominal paraaortic lymph node swelling, had their electronic medical charts reviewed. Pancreatic cancer (n = 41) was the major primary origin of pain.

Methods

Ethics

This clinical study was approved by the Institutional Review Board for Clinical Studies at the Shizuoka Cancer Center (#J2023-57-2023-1-3). After the IRB review, it was determined that consent to participate in the research would be approved by opting out, and that it was not necessary to obtain informed consent from the patients.

SNN Procedure

The lead author, who is a member of the palliative care team and a board-certified pain clinician with more than 25 years of clinical experience, performed all the procedures. The procedures were started at either 11:00 AM or 1:30 PM. If a patient received epidural analgesia, continuous injection of a local anesthetic was terminated before starting the procedure. SNN was performed with the patient prone. Under fluoroscopic guidance, the procedure was performed using a transdiscal approach and a 22G nerve block needle. All the patients were instructed to fast after 8:00 AM. SNN was performed in the morning (starting at 11:00) in 60 cases and in the afternoon (starting at 1:30) in 10 cases. In 14 cases (20%), continual epidural analgesia was administered until immediately before the SNN block to maintain analgesia and/or to diagnose visceral (sympathetic) pain.

All procedures were performed via an intervertebral disc approach at the T12/L1 intervertebral level in 66 cases or at the L1/L2 intervertebral level in 4 cases. Anhydrous ethanol injection (99.5%) was used as the neurolytic agent. One block needle was inserted from

one side to inject the contrast medium (iohexol), and when the spread to the contralateral retrocrural space (the other side of the aorta) was not enough, an additional second needle, if the other side of retrocrural space was intact, was inserted from the other side of the midline to supplement the spread. Patients were kept prone for one hour postprocedure. They then stayed in bed to rest until 9:00 AM the following morning, except when they were allowed to lift their heads up to an angle of 60° for eating or drinking.

Fluid Resuscitation Pre- and Post-SNN

Hemodynamic status was measured immediately preprocedure, every 5 minutes intraoperatively, immediately postprocedure, immediately after the patient returned to the ward, one hour postprocedure, then every 4 hours at 4:00 PM 8:00 PM on the day of the procedure and at midnight, 4:00 AM and 8:00 AM the following day.

Blood pressure and urine output were measured every 4 hours: at 4:00 PM and 8:00 PM on the day of the procedure and at midnight, 4:00 AM, and 8:00 AM the following day (a bladder catheter was placed in all patients to measure urine output).

All patients had their prophylactic fluid resuscitation started at 10:00 AM. One liter of low-molecular-weight dextran (LMWD) injection and one liter of lactated Ringer's solution (LRS) were administered intravenously in that order over a 24-hour period from 10 AM on the day of the block to 10 AM the following day. The first 500 mL of LMWD were administered over 4 hours if SNN was performed at 11:00 AM; it was administered over 6 hours if SNN was performed at1:30 PM.

Because some patients were receiving daily hyperalimentation or maintenance fluid therapy, the contents of the basic prophylactic fluid resuscitation for these patients were determined separately for each one (see Results). Oliguria and hypotension were defined as less than 100 mL/4hr of urine output and below 80 mmHg of systolic blood pressure, respectively.

When oliguria was observed at the points for urine output and blood pressure measurement every 4 hours, 250 mL of LRS as additional fluid was administered intravenously for one hour. When hypotension occurred, 250 mL of LRS was administered intravenously for one hour, followed by an 8 mg ephedrine hydrochloride injection.

Measurements

The following data were obtained for each patient: patient background including primary site of malignancy; clinical classification of pain mechanism; performance status (PS) (Eastern Cooperative Oncology Group [ECOG]); presence of diabetes mellitus; presence of hypertension; serum albumin level; hemoglobin level; hematocrit level; C-reactive protein level; estimated glomerular filtration rate; glomerular filtration ratio; presence of celiac plexus invasion and/or peritoneal dissemination; dose of neurolytic agent (anhydrous ethanol); postblock pyrexia; and survival time post-SNN.

Statistical analysis was performed by EZR software (Ver. 1.60, Jichi Medical University Saitama Medical Center)

The difference of measurements between the groups was evaluated by the Mann-Whitney U test except for peritoneal dissemination and celiac plexus invasion. The correlation between the presence or absence of peritoneal dissemination or celiac plexus invasion and the need for additional infusion was analyzed using Fisher's exact test. A significant difference was defined as $P < 0.05$.

Results

Patient Background (Table 1 and Fig. 1)

Sixty-eight patients who had a total of 70 procedures were included in the data analysis (2 patients received the procedure twice). Mean (SD) patient age was 62.5 (± 12.0) years, 33 (48.5%) were men, height and weight of the patients were 160.9 (± 9.4) cm and 50.4 (± 10.3) kg, respectively. The primary malignancy sites were the pancreatic body in 17 cases, the pancreatic head in 16 cases, the pancreatic tail in 8 cases, the stomach in 8 cases, the colon/rectum in 6 cases, the gallbladder/bile duct in 6 cases, the esophagus in 4 cases, and others in 5. There were 14 (20.0%) and 51 (72.9%) cases of peritoneal dissemination or celiac plexus invasion, respectively. Both diabetes

Table 1. *Patient characteristics*.

Peritoneal dissemination	Yes/No = 14/56 (Yes: 20.0%)			
Involvement of celiac plexus	Yes/No = 51/19 (Yes: 72.9%)			
Abdominal paraaortic metastasis	Yes/No = 18/52 (Yes: 25.7%)			
Diabetes mellitus	Yes/No = 27/43 (Yes: 38.6%)			
Hypertension	Yes/No = 27/43 (Yes: 38.6%)			
Total parenteral nutrition	Yes/No = 13/57 (Yes: 18.6%)			
Performance status (ECOG)	1	2	3	4
	1	34	22	13

ECOG: Eastern Cooperative Oncology Group

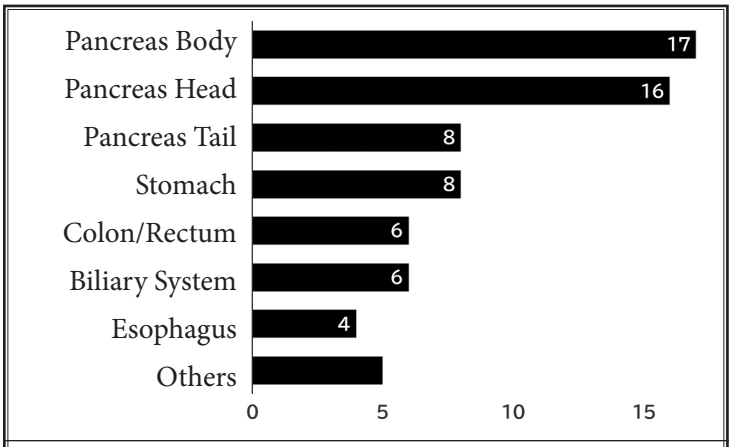


Fig. 1. *Primary malignancy sites.*

mellitus and hypertension were under treatment in 27 (39.7%) of the patients. High calorie infusions were administered in 10 cases (14.3%). Performance status (ECOG) 1, 2, 3 and 4 were in 1, 34, 22, and 13 cases, respectively.

Administered Neurolytic Agent Dose

The dose of anhydrous ethanol was 16.8 ± 2.6 mL (mean ± SD) (median: 16.0; rang: 10.0-20.0).

1. Post-SNN Survival Time
   Survival time from the SNN procedure to death was 132 ± 223 (mean ± SD) (median: 74; range: 11-1,558) days in 60 patients, excluding the survivors as of the end of February 2023.
2. Pre-SNN Supplemental Infusions to Compensate for Insufficient Daily Oral Intake

Three patients received one liter/d of high-calorie infusion or maintenance infusion and 10 other patients received 1,500 mL/d as hyperalimentation or maintenance fluid therapy because they could not have sufficient oral intake. Of these 13 patients, one patient received 500 mL of LMWD, 2 patients received one liter of LMWD, and 2 patients received one liter of LMWD plus 500 mL of LRS as supplemental fundamental infusion.

Post-SNN Additional Infusions to Compensate for Hypovolemia

Additional postprocedure infusions of Lactated-Ringer solution were administered to 14 patients due to decreased urine output. The additional infusion volumes were 250 mL (6 patients), 500 mL (4 patients), 750 mL (one patient), one liter (2 patients), and 1,250 mL (one patient). Hypotension was not observed in any patient.

Comparison of Patient Backgrounds and Measurement Values Between Groups

Comparison of ages, heights, weights, performance status, albumin levels, hemoglobin levels, hematocrit levels, urine outputs (during the 24-hour period from 10:00 AM on the day of SNN to 10:00 AM on the day after SNN) among the cases receiving additional fluid (14 cases) and those not receiving additional fluid (56 cases), along with their C-reactive protein and eGFR levels, performance status (ECOG), primary malignancy sites, complications such as peritoneal dissemination or celiac plexus invasion, continuous epidural anesthesia pre-SNN, doses of ethanol as the neurolytic agent, pyrexia within 24 hours post-SNN, urine outputs, and survival time post-SNN are shown in Table 2 and Figs. 2–4. There were no significant differences in the measurements between the 2 groups except the doses of the injected neurolytic agent (P = 0.038).

3. Fluid Resuscitation Adverse Events

No clinical signs of excessive fluid—such as pleural effusion and/or ascites, edema, or dyspnea—were observed.

Discussion

Epigastralgia and back pain associated with upper abdominal visceral malignancies, such as pancreatic cancer and/or paraaortic lymph node metastases, can become severe due to disease progression and resistance to analgesics, mainly opioids (11-14). In addition, side effects in the central nervous system, such as drowsiness and general malaise caused by opioid analgesics as well as gastrointestinal adverse events such as loss of appetite and constipation, may make it difficult to increase the dose of opioid analgesics, which may contribute to a significant decrease in the quality of life of the patient and the patient's family.

The splanchnic nerves are responsible for sympathetic pain from upper abdominal visceral lesions and/or stimulation of the sympathetic network surrounding the abdominal aorta caused by enlarged abdominal paraaortic lymph nodes. They consist of 3 pairs of left and right splanchnic nerves (major, minor, and least splanchnic nerves) connecting the right and left celiac plexuses to the fifth-to-twelfth thoracic sympathetic ganglia and the first lumbar ganglia (15).

Table 2. *Patient background in patients receiving additional fluid or not. Values are number, mean ± SD, range or median.*

	Additional fluid + (n = 14)	**Additional fluid - (n = 56)**
Age (y.o.)/Sex	65.8 ± 12.5* / Male : Female = 5 : 9	61.7 ± 12* / Male : Female = 28 : 38
Height (cm)/Weight (kg)	160.4 ± 10.1* / 65.8 ± 12.5*	160.4 ± 10.1* / 65.8 ± 12.5*
Diabetes Mellitus (cases)	Yes : No = 3 : 11 (Yes 21.4%)	Yes : No = 26 : 30 (Yes 46.4%)
Hypertension (cases)	Yes : No = 6 : 8 (Yes 42.9%)	Yes : No = 22 : 34 (Yes 39.3%)
Alb (g/dL)	3.3 ± 0.6*	3.2 ± 0.6*
Hemoglobin (g/dL) / Hematocrit (%)	10.9 ± 2.3* / 33.9 ± 6.6*	10.6 ± 2.1* / 32.1 ± 5.9*
CRP (mg/dL)	3.7 ± 5.3*	4.1 ± 4.6*
eGFR (mL/min/1.73m^2)	89.4 ± 27.1*	92.7 ± 30.3*
PS (ECOG)	1 : 2 : 3 = 7 : 3 : 4	0 : 1 : 2 : 3 = 1 : 27 : 19 : 9
Primary site of malignancy (cases)	Pancreas: 7; Colon/Rectum: 3; Stomach: 1; Gall bladder: 1; Lung: 1; Ovary: 1	Pancreas: 34; Biliary system: 5; Stomach: 1; Esophagus: 4; Others: 6
Peritoneal dissemination (cases)	Yes : No = 4 : 10 (Yes: 28.6%)	Yes : No = 14 : 42 (Yes: 25.0%)
Celiac plexus invasion (cases)	Yes : No = 13 : 1 (Yes: 92.9%)	Yes : No = 43 : 13 (Yes: 76.8%)
Continuous epidural analgesia before SNN	None	14 (25.0%)
Volume of neurolytic agent (mL)	18.1 ± 1.9* (15 ~ 20 median: 18 mL)	16.5 ± 2.6* (10 ~ 20 median: 16 mL)
Pyrexia (< 37.0°C)	Yes : No = 14 : 0 (Yes: 100%)	Yes : No = 45 : 11 (Yes: 80.4%)
Urine output after SNN (mL/24h)	1,018 ± 507 (median: 1,000 mL)	1,517 ± 764 (median: 1,400 mL)
Survival time from SNN (days)	152 ± 206* (11 ~ 798 median: 73)	125 ± 230* (11 ~ 1,558 median 74)

Additional fluid + : Patients who received additional fluid due to decrease in urine output (< 100mL/4 hours); Additional Fluid - : Patients who did not receive additional fluid. ECOG: Eastern Cooperative Oncology Group. SNN: splanchnic nerve neurolysis.

SNN is effective for upper abdominal visceral pain and visceral pain associated with enlarged abdominal paraaortic lymph nodes that enter the spinal cord via the celiac plexus and splanchnic nerves. It is indicated not only for patients who are refractory to pharmacotherapy, but also for opioid naïve patients and patients who require relatively low doses of opioids (1-10).

One of the most important points to keep in mind when performing SNN is that systemic hypotension may occur due to SNN's sympathetic blocking effect in addition to insufficient oral intake caused by cancer itself and/or appetite loss due to severe pain. The incidence of systemic hypotension has been reported as 21.4% (8) and 29% (6). This is a major SNN complication resulting from relative hypovolemia due to arterial dilatation, since the sympathetic nerves at the distal end of the splanchnic nerves innervate almost the entire upper abdominal gastrointestinal tract. There are currently no recommendations or guidelines regarding an infusion method. A sufficient volume of fluid should be ensured for the safe performance of SNN. yet

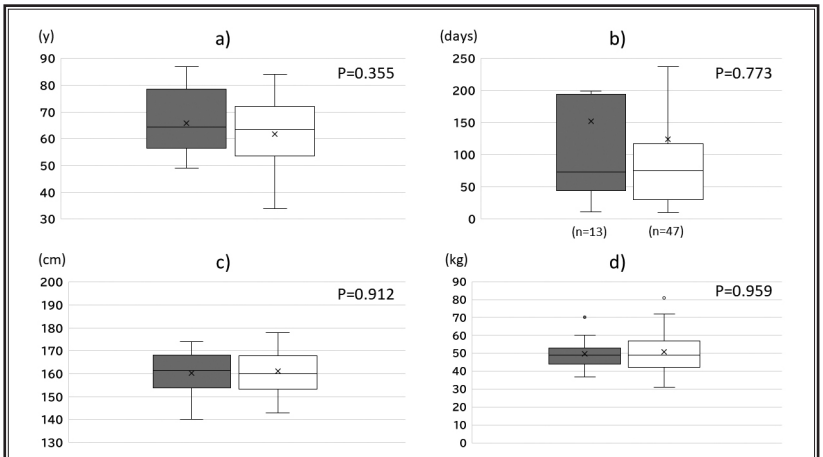


Fig. 2. *Comparison of patient backgrounds between the groups; black box: additional fluid (+) group (n = 14), white box: additional fluid (-) group (n = 56).*
a) age, b) survival time from SNN, c) height, d) weight

There are few clinical reports in the field. This is the major reason why we conducted this study. The type,

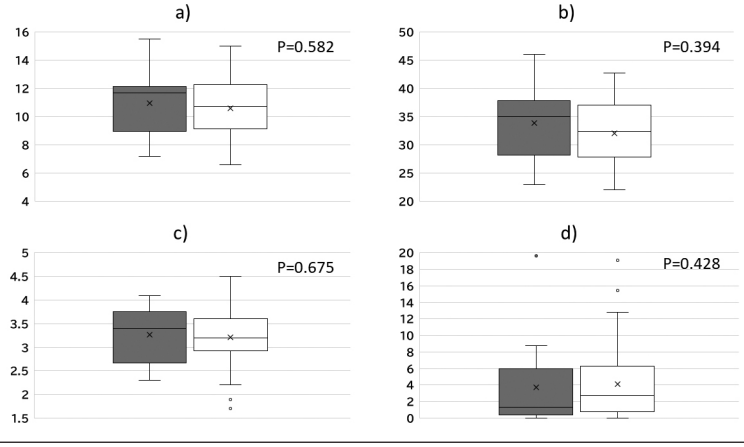
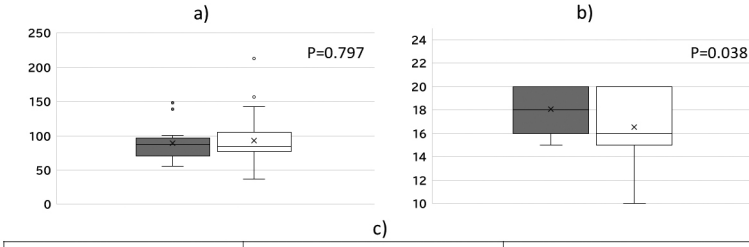


Fig. 3. *Comparison of patient backgrounds; black box: additional fluid (+) group (n = 14), white box: additional fluid (-) group (n = 56).*
a) hemoglobin concentration, b) hematocrit value, c) albumin level, d) C-reactive protein value



c)

	Additional fluid (+)	Additional fluid (-)
Peritoneal dissemination (Yes)	4/14 (29%)	14/56 (25%)
Celiac plexus invasion (Yes)	13/14 (93%)	43/56 (77%)

Fig. 4. *Comparison of patient backgrounds; black box: additional fluid (+) group (n = 14), white box: additional fluid (-) group (n = 56).*
a) estimated glomerular filtration ratio, b) volume of neurolytic agent (ethanol), c) presence of peritoneal dissemination and celiac plexus invasion

volume, and rate of administration of fundamental fluid resuscitation, as well as the criteria for additional infusions, were all based on the author's own clinical experiences. A total of 2 liters as fundamental fluid, which included one liter of LMWD and one liter of LRS, was administered over a 24-hour period from the day of the block to the following day. This prevented systemic hypotension without causing excessive fluid retention.

We defined oliguria as less than 100 mL of urine output in 4 hours; 250 mL of LRS was administered for one hour when it was observed. Blood pressure and urine output measurements were repeated every 4 hours in order to promptly manage hypovolemia. Although insufficient urine output was observed in 14 patients, no patients experienced systemic hypotension or associated symptoms. Furthermore, there were no signs of excessive fluid retention, such as heart failure symptoms or pleural effusion and/or ascites, due to the additional infusion. A useful assumption underlying these results is that our exclusion criteria included patients with impaired cardiopulmonary or renal functions, those with fluid retention in the thorax or abdomen, and those with systemic edema.

We did not find any indicators which would predict the need for additional fluid resuscitation post-SNN, except the volume of the administered neurolytic agent. Post-SNN hemodynamic status was carefully monitored in the patients who received a high volume of ethanol.

Limitations

The limitations of this study include, firstly, its retrospective design and that it was conducted at a single-center. Secondly, although the number of patients in this study was relatively large for a single-center clinical report of SNN, future studies with additional cases should be conducted. Such studies would contribute to establishing a more precise method of fluid resuscitation to avoid systemic hypotension induced by SNN.

Conclusion

As an SNN periprocedural fundamental fluid resuscitation, one liter of LMWD plus one liter of LRS in 24 hours from the day of the block to the following day, is considered sufficient and safe. In addition, 250 mL of additional infusion over an hour for a patient whose 4-hour urine output is less than 100 mL is also sufficient to prevent systemic hypotension. Although this pro-

phylactic fluid resuscitation may prevent hypotension, the necessity for additional fluid may increase when a higher volume of ethanol is administered as the SNN neurolytic agent.

Authors' Contribution

TS conceptualized the research, drafted the paper, and served as the research director.

YN, MS, RN, TS, YK, and RT collected data and critically reviewed the paper.

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