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A 5% Glucose Solution for the Liquid Formulation Gemcitabine Solvent Decreases Gemcitabine-induced Vascular Pain

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Abstract. *Background/Aim: Gemcitabine (GEM)-induced vascular pain often occurs in patients. A 5% glucose solution for the lyophilized formulation of GEM solvent is known to decrease the frequency of GEM-induced vascular pain compared with saline. In this study, we aimed to examine the availability of glucose for a liquid formulation GEM solvent for the prevention of GEM-induced vascular pain. Patients and Methods: In total, 214 patients with bile tract or pancreatic cancer, who received GEM-containing regimens, were enrolled in this retrospective study. The patients were divided into a glucose group, which was administered the liquid formation GEM diluted with glucose, and a saline group. The frequency of GEM-induced vascular pain was compared between them. Results: Glucose significantly decreased the frequency of GEM-induced vascular pain during the first GEM administration (36% vs. 55%, p=0.005). Conclusion: Switching the solution for liquid formulation GEM from saline to glucose significantly decreased the frequency of vascular pain.*

Gemcitabine (GEM) is widely used for the treatment of a variety of solid tumors, such as pancreatic cancer, bile tract cancer, and breast cancer, as monotherapy or in combination with other chemotherapies (1-3). Although GEM has relatively mild adverse events except for hematotoxicity, it induces vascular pain that arises during GEM infusion, which occurs in 30-40% of patients and is associated with deterioration in patients' quality of life (4). The mechanism of drug-induced vascular pain is unclear, but it is generally considered to be affected by pH or osmotic pressure (5). Vascular pain and vascular induration make a patient's peripheral vessel reservation difficult, but there are few established methods to deal with this condition. The original GEM (Gemcitabine® Eli Lilly, IN, USA) is a lyophilized formulation drug, but some generic drugs have GEM of liquid formulation that does not need to be dissolved for mixing in Japan (6, 7). The use of liquid formulation GEM is advantageous in terms of saving time for mixing, but a previous study reported that it induces more vascular pain compared with lyophilized formulation GEM, despite being dissolved with only water and pH buffer solution (8). The liquid formation GEM was adopted at Hokkaido University Hospital in July 2014, and many patients had experienced vascular pain, similar to previous reports (8, 9). On the other hand, a previous report revealed that the use of 5% glucose solution as the solvent of lyophilized formulation GEM significantly reduced the frequency of vascular pain compared to the use of saline solution, although its mechanism is unclear (9). Therefore, we hypothesized that a 5% glucose solution for the solvent of liquid formation GEM would reduce the frequency of vascular pain compared to saline solution, as we have observed that a dilute solution switch from saline to 5% glucose was successful in several cases. Consequently, at our hospital, we changed the GEM dilute solution from saline to 5% glucose in the GEM-containing chemotherapy regimens since July 2018. In this study, we examined the ability of a 5% glucose solution to prevent GEM-induced vascular pain.

Patients and Methods

Study design and patients. Patients who were administered the liquid formulation GEM (1,000 mg/m^2) for either bile tract or pancreatic cancer from July 2014 to October 2020 were enrolled in this retrospective observational study (Figure 1). Patients who were previously administered GEM, had an inserted central venous (CV)

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port, and those without sufficient information were excluded. The patients were divided into two groups: a 5% glucose solution group (from July 2018 to October 2020) and a saline solution group (from July 2014 to December 2019). This study was approved by the Institutional Review Board of Hokkaido University Hospital (approval number: 019-0033), and all procedures were performed in accordance with the Declaration of Helsinki. In view of the retrospective nature of the study, written informed consent from the subjects was not necessary.

Treatment. All patients received any of the five GEM-containing chemotherapies as follows: 1) GEM alone (1,000 mg/m^2 on days 1, 8, and 15, every 4 weeks), 2) GEM + S-1 (a compounding agent of tegafur, gimeracil, and oteracil potassium) (GEM 1,000 mg/m^2 on days 1 and 8 + S-1 80 mg/m^2/day on days 1-14, every 3 weeks), 3) GEM + cisplatin (CDDP) (GEM 1,000 mg/m^2 and CDDP 25 mg/m^2 on days 1 and 8, every 3 weeks), 4) GEM + CDDP + S-1 (GEM 1,000 mg/m^2 and CDDP 25 mg/m^2 on day 1, and S-1 80 mg/m^2/day on days 1-7, every 2 weeks), and 5) GEM + nanoparticle albumin-bound paclitaxel (nab-PTX) (GEM 1,000 mg/m^2 and nab-PTX 125 mg/m^2 on days 1, 8, and 15, every 4 weeks). The dosage of anticancer agents was modified at the discretion of the clinicians according to the patient's condition. The liquid formulation GEM was prepared in a total volume of 100 ml diluted with 5% glucose or saline solution, and intravenously administered into the most suitable peripheral vessel selected by nurses for 30 min. All patients intravenously received the appropriate antiemetic premedication consisting of dexamethasone (DEX) (6.6 mg) for the GEM alone and GEM + S-1 groups, or a combination of DEX (9.9 mg) and palonosetron (0.75 mg) for the GEM + CDDP, GEM + CDDP + S-1, and GEM + nab-PTX groups in accordance with the National Antiemetic Guidelines of the Japanese Society of Clinical Oncology (10).

Evaluation criteria. The primary endpoint of this study was to compare the frequency of vascular pain during the first GEM infusion between the 5% glucose and saline groups. The secondary endpoint was to compare the frequency of vascular induration after the first GEM administration, the frequency of vascular pain, and vascular induration during the six GEM administrations between the two groups. The evaluation period included six GEM administrations as the general first evaluation of efficacy was approximately 2-3 months after the initiation of chemotherapy. This retrospective and observational study was conducted at the Hokkaido University Hospital using data from electronic medical records, and the assessment of vascular pain and induration in each patient were conducted depending on the physicians' and nurses' observations, in addition to the patient's complaint. In case of vascular pain that emerged during GEM administration, a hot compress was routinely conducted based on the nurses' decisions.

Statistical analysis. We hypothesized that the frequency of vascular pain would reach 40% in the 5% glucose group and 60% in the saline group based on a previous study (9), and the total sample size of 214 was calculated under the conditions of 80% power and 0.05 significance level, with a patient ratio of 1:1. The differences in the baseline clinical characteristics between the saline and 5% glucose groups were assessed using Fisher's exact test for categorical outcome variables and the Mann-Whitney *U*-test for continuous parameters. Vascular pain and vascular induration frequency between the two groups were compared using Fisher's exact test. Univariate and multivariate analyses were performed using logistic analysis to reveal the independent risk factors for vascular pain during the first GEM administration, using the following covariates: sex, age, body mass index (BMI), GEM dose, DEX dose, and the administration of analgesic. We referred to previous reports to select these factors (5, 8). Variables that demonstrated potential associations with incidence in the univariate logistic regression analysis ($p<0.10$) were considered when building the multivariable model. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is an R graphical user interface software (The R Foundation for Statistical Computing, Vienna, Austria) (11). More precisely, it is a modified version of R commander designed to add the statistical functions frequently used in biostatistics. Statistical significance was set at $p<0.05$.

Results

Patient characteristics. Patient characteristics at baseline are shown in Table I. There were no significant differences in sex, age, BMI, body surface area (BSA), GEM dose, cancer type, chemotherapy regimen, and concomitant drugs between the two groups.

Evaluation of vascular pain and duration. The frequency of GEM-induced vascular pain during the first GEM administration is shown in Figure 2. The frequency of vascular pain was 55% in the saline group and 36% in the 5% glucose group, suggesting that diluting GEM with 5% glucose solution significantly decreased its frequency compared with saline ($p=0.005$). The frequency of GEM-induced vascular pain during the six times GEM administration was 75% in the saline group and 49% in the 5% glucose group, with significant improvement in the 5% glucose solution ($p=0.001$, Figure 3). In addition, we evaluated the frequency of vascular induration in both the first and initial six rounds of GEM administration. However, there was no statistical difference between the saline group and the 5% glucose group both in the first GEM administration (17.8% *vs*. 19.6%, $p=0.86$) and the initial six administrations (46.7% *vs*. 59.8%, $p=0.07$).

Univariate and multivariate analyses for vascular pain frequency during the first GEM administration. The results of the univariate and multivariate analyses for risk or preventive factors for the frequency of vascular pain at first GEM administration are shown in Table II. Five percent glucose solution and patients aged ≥65 years were identified as preventive factors for GEM-induced vascular pain frequency.

Discussion

Vascular pain is one of the most discomforting adverse effects caused by GEM administration, but there are few reports regarding its solution. Previous studies reported that liquid formulation GEM induces more severe vascular pain than the

Table I. *Patient characteristics*.

	Saline group (n=107)	5% Glucose group (n=107)	*p*-Value
Gender (male/female)	71/36	62/45	0.26
Age (years) [median, range]	69 [44-84]	70 [38-91]	0.67
BMI (kg/m^2) [median, range]	21.16 [16.26-29.43]	21.64 [14.82-45.73]	0.25
BSA (m^2) [median, range]	1.57 [1.27-2.04]	1.55 [1.17-2.28]	0.44
GEM dose (mg) [median, range]	1,500 [1,000-2,000]	1,520 [980-2,160]	0.55
Cancer type			
Pancreatic	83	82	
Bile tract	24	25	1.00
Chemotherapy regimen			
GEM alone	25	11	
GEM+S-1	13	13	
GEM+CDDP	14	10	
GEM+CDDP+S-1	4	10	
GEM+nab-PTX	51	63	0.09
Concomitant drug			
Analegesic	30	23	0.34
Hyperlipidemic drug	19	27	0.24
Antidiabetic drug	30	30	1.00
Antihypertensive drug	37	34	0.77
Anticoagulant	20	11	0.12
Cardiovascular drug	14	7	0.17

GEM: Gemcitabine; CDDP: cisplatin; BSA: body surface area; nab-PTX: nanoparticle albumin-bound paclitaxel; BMI: body mass index; S-1: a compounding agent of tegafur, gimeracil, and oteracil potassium.

lyophilized formulation GEM (8), and the use of 5% glucose solution for the solvent in lyophilized formulation GEM significantly reduced the frequency of vascular pain compared to the use of saline solution (9). Therefore, we examined the use of a 5% glucose solution for diluting liquid formulation GEM as prophylaxis against GEM-induced vascular pain.

Our study results indicated that the use of 5% glucose solution for diluting liquid formulation GEM significantly decreased the frequency of vascular pain not only for the first time but also for the six times of GEM administration compared to the use of saline. In contrast, switching from saline to 5% glucose solution did not affect the frequency of GEM-induced vascular induration. As vascular induration by chemotherapy is greatly affected by patient-related' factors, such as the puncture site, method used, and patient body motion (12), we assume that they have a greater impact than solution switching.

The mechanisms underlying GEM-induced vascular pain are not fully understood. Vascular pain is generally considered to be caused by low pH or high osmotic pressure (9). Nagata *et al*. showed that the liquid formulation of epirubicin is associated with a significantly higher risk off venous irritation compared to the lyophilized formulation (13); the pH of the liquid formulation epirubicin was lower than that of the lyophilized formulation when it was diluted with saline (pH range, 2.5-3.5, and 4.5-6.0, respectively). However, the pH of the liquid formulation GEM is slightly lower than that of the lyophilized formulation GEM (pH range, 2.0-2.8 and approximately 3.0, respectively) (6, 7). In addition, Nagai *et al*. reported that the pH of lyophilized formulation GEM diluted with 5% glucose solution is similar to that with saline (both pH ranges were around 3.0) (9). With regard to osmotic pressure, that of liquid formulation GEM was lower than that of lyophilized formulation GEM (6, 7), and another report revealed that the osmotic pressure of GEM diluted with 5% glucose solution is higher than that with saline (9). Accordingly, we consider that there is no relationship between GEM-induced vascular pain and both pH and osmotic pressure. We investigated other factors that can influence GEM-induced vascular pain, suggesting that β-uridine, which is a GEM contaminant, may affect GEM-induced vascular pain. Kuwahara *et al*. reported that β-uridine existed in liquid formation GEM immediately after dissolution in saline, whereas it was not detected in lyophilized formulations (14). We speculate that β-uridine may be one of the factors for vascular pain, although there are no reports regarding its toxicity in humans. In addition, it is suggested that glucose itself might have an analgesic effect, as oral administration of glucose or sucrose solutions provides effective analgesia for procedural pain in neonates (15). However, Kracke *et al*. reported that glucose does not directly interact with mu opioid receptors in an *in vitro* experiment (16); this possibility is still unclear. Further studies are needed to reveal the exact

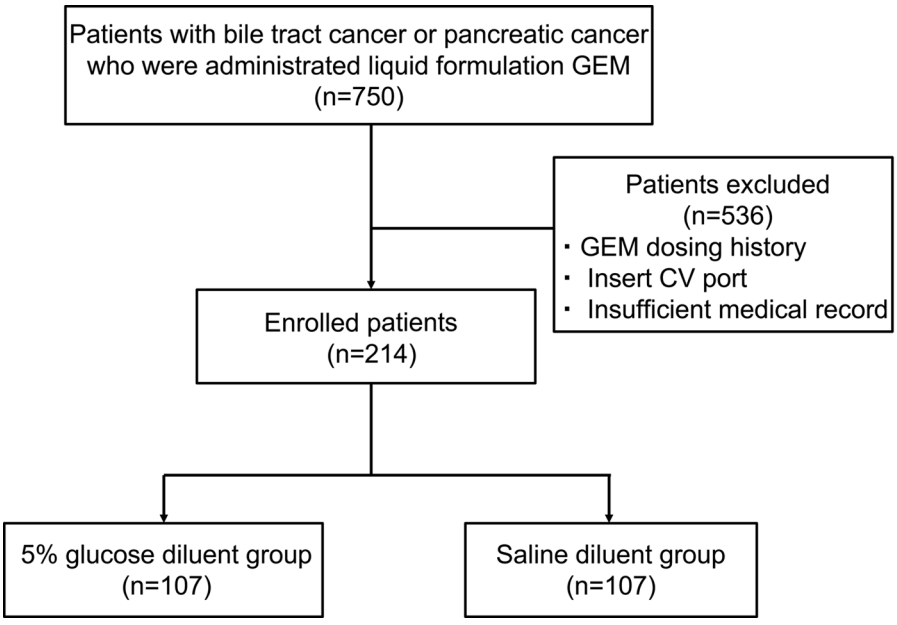

Figure 1. *Study design. GEM: Gemcitabine; CV: central venous.*

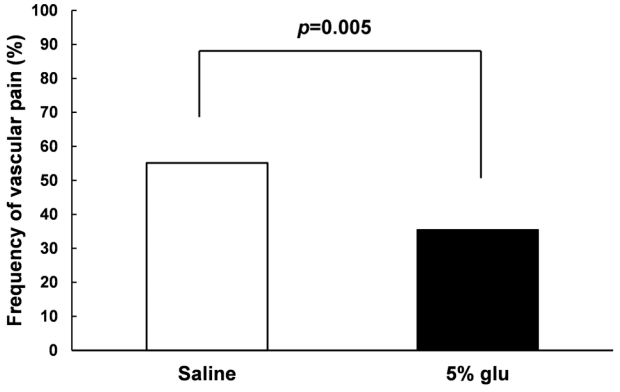

Figure 2. *Comparison of the frequency of gemcitabine-induced vascular pain between the saline and 5% glucose (5% glu) solution groups during first administration.*

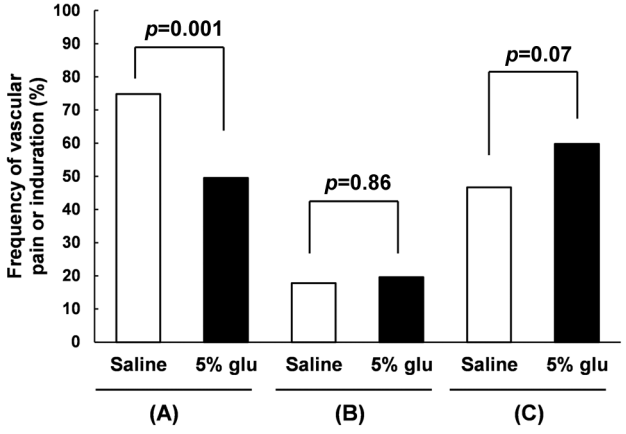

Figure 3. *Comparison of the frequency of (A) gemcitabine (GEM)-induced vascular pain until the sixth GEM administration, (B) GEM-induced vascular induration for the first GEM administration, and (C) until the sixth GEM administration between the saline and 5% glucose (5% glu) solution groups.*

mechanisms of GEM-induced vascular pain and its attenuation by a 5% glucose solution for better management.

General reported methods to treat vascular pain include hot compression, DEX mixing, line flashing by saline or 5% glucose, shortening injection time, and CV port insertion (8, 9, 13, 17, 18). Among them, DEX has various medical efficacies, such as anti-inflammatory and antiemetic effects. In addition, it is alkaline with pH 7.0 to 8.5 (19). Hata *et al*. reported that the combination of DEX 1.65 mg and oxaliplatin diluted with 250 ml of 5% glucose solution can reduce oxaliplatin-induced vascular pain as it increases pH (pH range from 4.7 to 6.7-7.3) (18, 20). On the other hand, Yoshiura *et al*. reported that the addition of DEX 0.875 mg to lyophilized formulation GEM diluted with 5% glucose solution does not affect the pH (pH range from 2.0-2.8 to 2.6-2.8) (19). However, we also speculate that the combination of higher dosage DEX to GEM solution may contribute to the alleviation of GEM-induced vascular pain because it was successful in preventing vascular pain in cases of oxaliplatin and epirubicin (18, 21).

Table II. *Univariate and multivariate analyses of factors associated with the frequency of gemcitabine-induced vascular pain at first administration.*

		Univariate analysis		Multivariate analysis	
	Vascular pain frequency (n, %)	Odds ratio [95%CI]	*p*-Value	Odds ratio [95%CI]	*p*-Value
Gender					
Female	45 (55.6%)				
Male	52 (39.1%)	1.94 [1.07-3.54]	0.02*	1.84 [0.92-3.67]	0.08
Age (years)					
≥65	64 (41.3%)				
<65	33 (55.9%)	0.56 [0.29-1.06]	0.07	0.41 [0.21-0.79]	0.008**
BMI (kg/m^2)					
≥22	33 (38.4%)				
<22	64 (50.0%)	0.62 [0.34-1.13]	0.12	Excluded	-
GEM dose					
≥1,500 mg	47 (39.2%)				
<1,500 mg	50 (53.1%)	0.57 [0.32-1.01]	0.05	0.69 [0.35-1.35]	0.28
DEX dose					
9.9 mg	63 (41.2%)				
6.6 mg	34 (55.7%)	0.56 [0.29-1.06]	0.07	0.55 [0.29-1.04]	0.07
Administration of analgesics					
Present	24 (45.3%)				
Absent	73 (45.3%)	1.00 [0.51-1.95]	1.00	Excluded	-
Solvent					
5% glucose	38 (35.5%)				
Saline	59 (55.1%)	0.45 [0.25-0.80]	0.006**	0.40 [0.22-0.72]	0.002**

DEX: Dexamethasone; GEM: gemcitabine; BMI: body mass index. *p<0.05, **p<0.01.

In our multivariate analysis, we also identified that patients aged ≥65 years had a lower risk of vascular pain frequency. Older age is associated with a lower incidence of pain, which may be caused by age-related weakening of nociceptive pathways (22). On the other hand, previous studies reported that female sex is a significant risk factor for GEM-induced vascular pain (5, 23), and our study suggested that there tended to be a relationship between gender and GEM-induced vascular pain, but this was not statistically significant. We anticipate that differences in blood vessel structure between sexes may be an element. In addition, our study indicated that a higher DEX dosage may reduce GEM-induced vascular pain. In a fundamental study using rabbits, DEX administration significantly decreased vinorelbine-induced phlebitis due to its anti-inflammatory effect (24). Accordingly, it may be possible to consider that a higher DEX dosage in antiemetic premedication decreases the risk of GEM-induced vascular pain.

The present study has several limitations. First, this was a retrospective study and employed a relatively small patient population from a single institution; therefore, it is necessary to conduct a multicenter, large-scale prospective study to confirm these results. Second, the evaluation of vascular pain in this study was not severe. To obtain further reliable results, the quantitative evaluations of patients on the visual analogue or numerical rating scale are needed.

In conclusion, the results of our study reveal that switching the solution for the liquid formulation of GEM from saline to 5% glucose significantly decreases the frequency of GEM-induced vascular pain. However, further prospective studies are necessary to elucidate the mechanism associated with this process.

Conflicts of Interest

KU, YS, TS, YT, and MS have no conflicts of interest in relation to this study. YK reports honoraria from Pfizer, Novartis, and Bayer, and research funding from Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Bayer, Chugai Pharma, Yakult, and Taiho, having provided speaker services for Eli Lilly, Chugai Pharma, Novartis, Pfizer, Bayer, and Taiho.

Authors' Contributions

Participated in research design: KU, YS, and TS. Conducted experiments: KU and YS. Performed data analysis: KU and YS. Wrote or contributed to the writing of the manuscript: KU, YS, YT, YK, and MS.

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