Original Article

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The Effects of Dokhwaljihwang-tang Intravenous Pharmacopuncture on Cisplatin-Induced Emesis and Gastrointestinal Mobility Disorder in Rats

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[Abstract]

Objectives : The objective of this study was to evaluate the effect of Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture on cisplatin-induced emesis and gastric mobility disorder in Wistar rats.

Methods : Thirty rats were randomly divided into six groups and cisplatin was administered to all groups except the normal group. The cisplatin group (n=5) received a cisplatin injection only. The saline group (n=5) was injected with cisplatin followed by 0.4 mL of saline. Groups DJT-1, DJT-2, and DJT-3 were injected with cisplatin, followed by 0.315 g/kg, 0.104 g/kg, and 0.034 g/kg of DJT, respectively. Body weight, food intake, and kaolin intake of rats were measured 12 h, 24 h, and 36 h after cisplatin injection. Residual food in the stomach was measured 48 h after cisplatin injection.

Results : There was no significant difference in weight. The food intake was not significantly different 12 h after cisplatin administration. All groups except the normal group showed significantly decreased food intake after 24 h. After 36 h, food intake was not significantly different between groups DJT-1, DJT-2, and DJT-3 and the normal group. The kaolin intake of groups DJT-1 and DJT-2 was significantly decreased at 12 h and 24 h after cisplatin injection. Kaolin intake and residual food in the stomach were significantly decreased in groups DJT-1, DJT-2, and DJT-3.

Conclusion : In a Wistar rat model, DJT intravenous pharmacopuncture is suggested to be effective for cisplatin-induced emesis and gastric motility disorder. In the future, it is necessary to study the mechanism and chemical composition of each individual constitutive drug.

Key words :
Dokhwaljihwang-tang;
Intravenous pharmacopuncture;
CINV;
Cisplatin;
Experimental study

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I. Introduction

Cancer cells originate from normal cells that have undergone abnormal division and proliferation as a result of stimulus of the genes that regulate cell proliferation[1]. Treatment of cancer includes surgery, radiation therapy, and/or chemotherapy. Radiation may affect normal cells and result in side effects such as bone marrow function depression, immunodeficiency, suppression of bone marrow hematopoiesis, erectile dysfunction and infertility, and skin changes[2]. Typical side effects of chemotherapy include fatigue, nausea, vomiting, diarrhea, reproductive dysfunction, hair loss, pain, and leukopenia. Among these, symptoms of gastrointestinal disorders such as anorexia, nausea, and vomiting occur most frequently[3].

Chemotherapy often results in nausea and vomiting (chemotherapy-induced nausea and vomiting, CINV)[4]. CINV occurs in as many as 70% to 80% of patients undergoing chemotherapy[5]. In Korea, the Seoul Asan Cancer Center guidelines were published in 2009, but there is still a lack of research on transition rates and therapeutic effect[6]. To alleviate CINV, various therapies such as psychotherapy, behavior therapy, and neurostabilizers such as antiepileptic drugs have been tried in addition to gastrointestinal drug therapy, but these methods are not always effective[7,8,9].

There have been many studies related to treatment of CINV in Korea, mostly of oral medications. However, patients undergoing chemotherapy usually have difficulty taking oral medications due to severe nausea and vomiting[10,11].

Dokhwaljihwang-tang (DJT) is used in gastrointestinal motility disorders in clinical practice; it is a Sasang prescription used for gastrointestinal problems in Soyangin[12]. Animal studies have reported that oral administration of DJT is effective for vomiting and nausea induced by the anticancer drug cisplatin[13]. Based on this previous research, we chose DJT for the present study.

The same effects as oral administration of a herbal medicine can be achieved with only a small amount of intravenous pharmacopuncture, with faster results[14]. Based on the positive outcomes of previous intravenous pharmacopuncture studies, we hypothesized that DJT intravenous acupuncture was likely to be effective in treating CINV. However, to the best of our knowledge, no such study has been performed. The objective of the present study was to evaluate the effect of DJT intravenous pharmacopuncture on cisplatin-induced emesis and gastric mobility disorder in Wistar rats.

II. Method

1. Animals

Seven-week-old male Wistar rats (mean weight 252.5±9.90 g, DBL, Chungcheongbuk-do, South Korea) were used. The incubation room was maintained at a temperature of 22 ± 2℃ and a humidity of approximately 40% to 60% in a light/dark cycle of 12 h/12 h. All rats were fed a standard solid food (Samtako, Osan, Korea), kaolin food (Junsei, Tokyo, Japan), and water, and adapted to the laboratory environment and kaolin food for one week before being used in the experiment. This experiment was conducted with the approval of O University Animal Experimental Ethics Committee (approval number DJUARB2016-001).

2. Kaolin

Kaolin feeds were prepared according to the method of Yamamoto et al[15]. First, 1% arabic gum (Junsei, Tokyo, Japan) was added to chemical pure grade kaolin (Junsei, Tokyo, Japan) and then mixed with primary distilled water and kneaded into a similar weight and shape as the conventional solid food.

3. Pharmacopuncture manufacture

Table 1 summarizes the pharmacological composition of the DJT used in the present study. The materials were purchased from Okcheon-dong (Busan, Korea). The medicinal material was washed in an ultrasonic cleaner for 60 min and allowed to dry completely at room temperature before use. In total, 144 g of DJT medicinal material was finely cut and placed a flask with 1440 mL of 70% ethanol solution for 1 h at 80℃. The extract was filtered with filter paper (No. 1 Filter Paper, Whatman, USA), and the filtrate was concentrated under reduced pressure using a vacuum concentrator. In total, 33.48 g of extract was obtained, with a yield of 23.25%. The extract was stored at -20℃ (Fig. 1).

The extracted DJT was diluted into normal saline at three concentrations, and then filtered through a 0.22 nm membrane on a clean bench to be used as intravenous pharmacopuncture. Intravenous pharmacopuncture solutions were used immediately after preparation. A disposable syringe was used for injection.

Table 1. The composition of Dokhwaljihwang-tang

Herbs	Pharmacognostic name	Dosages (g)
熟地黃	*Rehmanniae Radix Preparata*	16
山茱萸	*Corni Fructus*	8
茯苓	*Hoelen*	6
澤瀉	*Alismatis Rhizoma*	6
獨活	*Angelicae Pubescentis Radix*	4
牧丹皮	*Moutan Cortex Radicis*	4
防風	*Ledebouriellae Radix*	4
Total amount		48

4. Classification and treatment of experimental groups

Thirty Wistar rats were randomly divided into six groups: normal, cisplatin, saline, DJT-1, DJT-2, and DJT-3 (five rats in each group). The normal group did not undergo any treatment. The cisplatin group underwent an intraperitoneal injection of cisplatin only. The saline group was injected intraperitoneally with cisplatin followed by 0.4 mL of saline through the tail vein. The remaining three groups were administered cisplatin intraperitoneally, then injected in the tail vein with 0.4 mL of 0.315 g/kg (group DJT-1), 0.104 g/kg (group DKT-2), or 0.034 g/kg (group DJT-3) of DJT pharmacopuncture solution.

5. Injection of intravenous saline and DJT pharmacopuncture

Immediately after cisplatin injection, the rat was fixed to a specially made restrainer. The tail was exposed to the outside of the restrainer, and 0.4 mL of DJT pharmacopuncture solution was injected through the tail vein of the rat. The saline group was injected with the same amount of normal saline in the same manner as the DJT group.

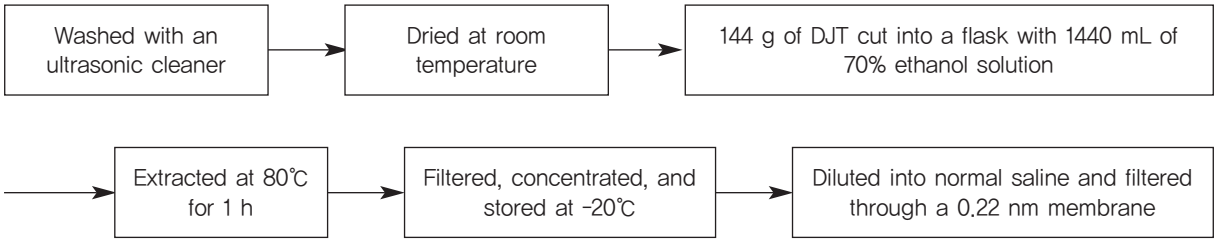

Fig. 1. Pharmacopuncture Manufacture

DJT, Dokhwaljihwang-tang.

6. Data measurement

1) Weight

Rats were weighed to the nearest 0.5 g using an electronic scale (CAS, East Rutherford, NJ, USA) before injection with cisplatin and at 12 h, 24 h, and 36 h after cisplatin injection.

2) Food intake

The remaining food was weighed to the nearest 0.001 g using an electronic scale (Mettler-Toledo, Columbus, OH, USA) just before cisplatin injection and at 12 h, 24 h and 36 h after cisplatin injection.

3) Kaolin intake

The remaining kaolin food was weighed to the nearest 0.001 g using an electronic scale (Mettler-Toledo) just before cisplatin injection and at 12 h, 24 h, and 36 h after cisplatin injection.

4) Residual food in the stomach

To determine how much residual food was in the stomach, the animals were fasted for 12 h from 36 h after cisplatin injection. At 48 h after cisplatin injection, the rats were anesthetized with diethyl ether and cervical dislocation was performed. Then, the skin and peritoneum were incised along the midline of the abdomen and the stomach was exposed. The entire stomach was removed from the abdominal cavity. After incising the stomach along the line connecting the esophagogastric junction and the pylorus, the remaining food residue in the stomach was collected on a plate and the water was removed and weighed to the nearest 0.001 g using an electronic scale (Metter-Toledo).

7. Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (IBM, USA). All results were expressed as mean ± standard error. The Kruskal-Wallis test and the Mann-Whitney U test were used to compare the groups. Statistical significance was set at 0.05.

III. Result

1. Weight change

After cisplatin injection, there was no significant different in weight among groups (Fig. 2).

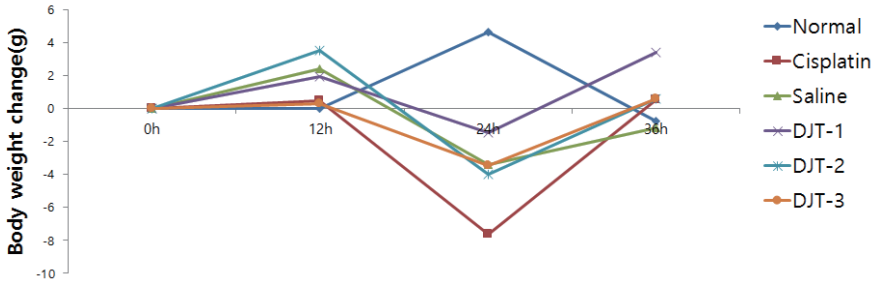

Fig. 2. Body Weight Change after Cisplatin Injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Body weight change was monitored every 12 h after cisplatin injection.

Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).

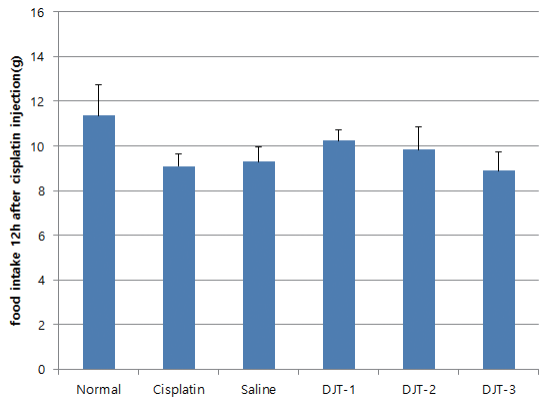

Fig. 3. Food intake 12 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Food intake was monitored at 12 h after cisplatin injection. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).

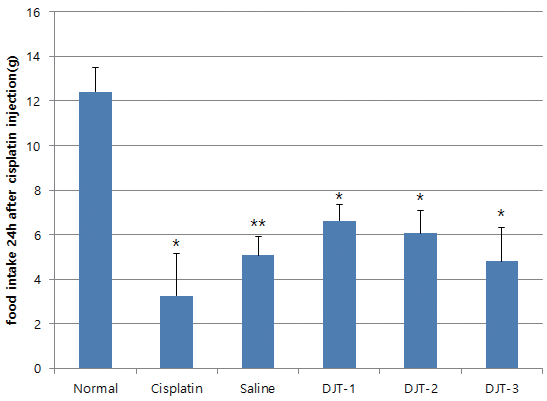

Fig. 4. Food intake 24 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Food intake was monitored from 12 h to 24 h after cisplatin injection. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).
*$p<0.05$, **$p<0.01$ vs. normal group by Mann-Whitney U test.

2. Food intake

1) Food intake 12 h after cisplatin injection

At 12 h after cisplatin injection, there was no significant difference in food intake among groups (Fig. 3).

2) Food intake 24 h after cisplatin injection

Compared with the normal group, all treatment groups showed a significant decrease in food intake 24 h after cisplatin injection (Fig. 4).

3) Food intake 36 h after cisplatin injection

Food intake was significantly decreased in the cisplatin group compared with that in the normal group at 36 h after cisplatin injection. The cisplatin, saline, DJT-1, DJT-2, and DJT-3 groups did not show a significant difference in food intake (Fig. 5).

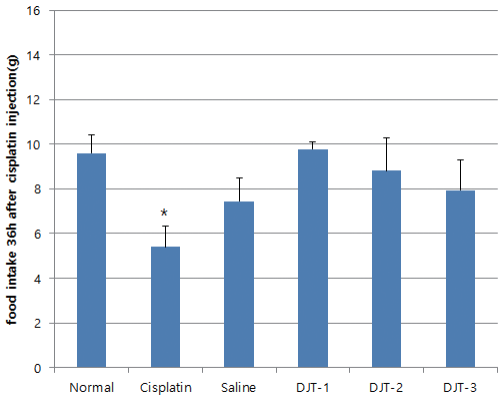

Fig. 5. Food intake 36 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Food intake was monitored from 24 h to 36 h after cisplatin injection. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).
*$p<0.05$ vs. normal group by Mann-Whitney U test.

3. Kaolin intake

1) Kaolin intake 12 h after cisplatin injection

The cisplatin and saline groups showed a significant increase in kaolin intake compared with the normal group 12 h after cisplatin injection. The kaolin intake of the DJT-1 and DJT-2 groups was significantly lower than that of the saline group (Fig. 6).

2) Kaolin intake 24 h after cisplatin injection

Kaolin intake in the cisplatin and saline groups was significantly increased compared with the normal group at 24 h after cisplatin injection. The kaolin intake of the DJT-1 and DJT-2 groups was significantly lower than that of the cisplatin and saline groups (Fig. 7).

3) Kaolin intake 36 h after cisplatin injection

The kaolin intake of the cisplatin and saline groups was significantly increased compared with the normal group at 36 h after cisplatin injection. The kaolin intake of the DJT-1, DJT-2, and DJT-3 groups was significantly lower than that of saline group (Fig. 8).

4. Remaining food in stomach

Compared with the normal group, the cisplatin and saline groups showed a significant increase in stomach contents. The DJT-1 group had a significant decrease in stomach contents compared with the cisplatin group. The DJT-2 and DJT-3 groups had significantly less food left in their stomachs than the cisplatin and saline groups (Fig. 9).

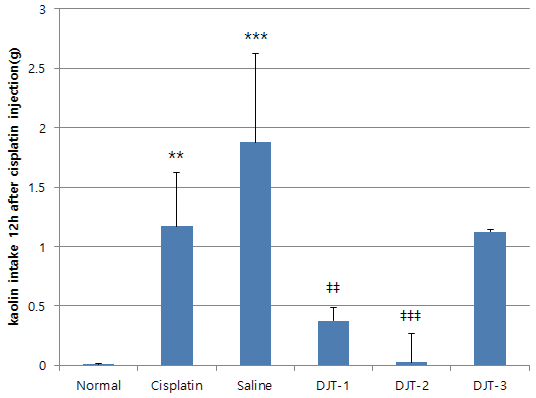

Fig. 6. Kaolin intake 12 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Kaolin intake was monitored for 12 h after cisplatin injection. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).
$^{**}p<0.01$, $^{***}p<0.001$ vs. normal group by Mann-Whitney U test.
$^{‡‡}p<0.01$, $^{‡‡‡}p<0.001$ vs. saline group by Mann-Whitney U test.

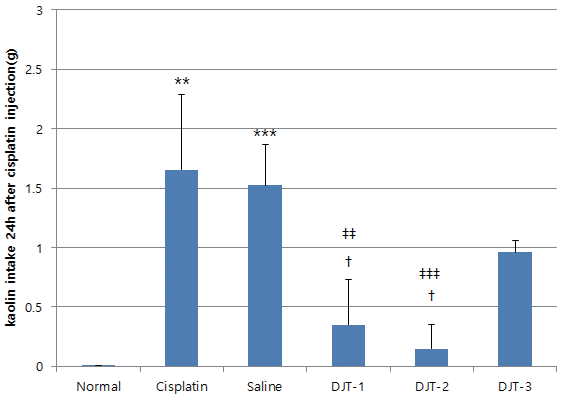

Fig. 7. Kaolin intake 24 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Kaolin intake was monitored from 12 h to 24 h after cisplatin injection. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).
$^{**}p<0.01$, $^{***}p<0.001$ vs. normal group by Mann-Whitney U test.
$^{†}p<0.05$ vs. cisplatin group by Mann-Whitney U test.
$^{‡‡}p<0.01$, $^{‡‡‡}p<0.001$ vs. saline group by Mann-Whitney U test.

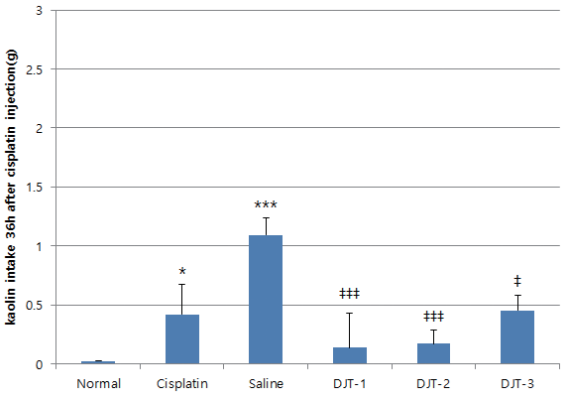

Fig. 8. Kaolin intake 36 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. Kaolin intake was monitored from 24 h to 36 h after cisplatin injection. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
DJT-2: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.104 g/kg).
DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).
*$p<0.05$, ***$p<0.001$ vs. normal group by Mann-Whitney U test.
‡$p<0.05$, ‡‡‡$p<0.001$ vs. saline group by Mann-Whitney U test.

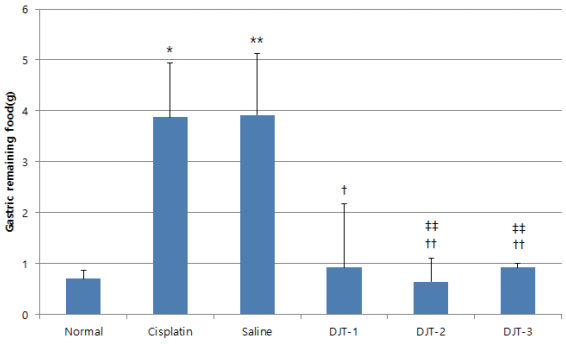

Fig. 9. Amount of food remaining in stomach at 48 h after cisplatin injection

Rats were treated with Dokhwaljihwang-tang (DJT) intravenous pharmacopuncture after cisplatin injection. At 48 h after cisplatin injection, the rats were sacrificed and the amount of gastric remaining food was measured. Each value and vertical bar represent mean ± standard error (n=5).
Normal: Rats with no treatment.
Cisplatin: Rats treated with cisplatin (7 mg/kg).
Saline: Rats treated with cisplatin (7 mg/kg) and saline (0.4 mL) injection.
DJT-1: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.315 g/kg).
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DJT-3: Rats treated with cisplatin (7 mg/kg) and DJT intravenous pharmacopuncture (0.4 mL, 0.034 g/kg).
*$p<0.05$, **$p<0.01$ vs. normal group by Mann-Whitney U test.
†$p<0.05$, ††$p<0.01$ vs. cisplatin group by Mann-Whitney U test.
‡‡$p<0.01$ vs. saline group by Mann-Whitney U test.

IV. Discussion

There are many studies of herbal medicines for the treatment of chemotherapy side effects[16,17,18]. Most of the existing treatment is administered orally; however, injected medications do not go through the digestive system, and their effect is faster than that of orally administered drugs[19,20]. Furthermore, larger amounts of oral medications are required because they undergo complicated metabolic processes compared with intravenous administration, and the rate of absorption is also lower than that of the intravenous injection.

Studies of herbal treatment for CINV and chemotherapy-associated gastrointestinal disorders include a comparison of general acupuncture therapy and Hominis Placenta pharmacopuncture therapy on severe dyspepsia[21]; Calculus Bovis from *Bos taurus*, Fel Ursi from *Ursus arctos*, and Hominis Placentapepsia for functional dyspepsia[22]; Ganoderma lucidum pharmacopuncture for chronic gastric ulcers in rats[23]; and Coptidis rhizome pharmacopuncture extract on acute gastritis[24]. However, studies of Sasang constitutional medicine are limited compared with those of other herbal medicines. In Sasang constitutional medicine, theoretically, So-eum types tend to have more digestive problems than other types. Accordingly, many digestive system studies of Sasang constitutional medicine are on So-eum-type medicines. However, many Soyang-type people also suffer from digestive problems[25].

DJT is one of the Soyang-type medicines used to treat digestive dysfunction. DJT studies are lacking compared with So-eum-type medicines.

Until recently, most DJT-related studies were case reports. To the best of our knowledge, there are no published studies of DJT intravenous pharmacopuncture, and studies of the mechanism of DJT are insufficient.

According to a recent study of DJT in the treatment of gastrointestinal disorders, serotonin and serotonin-inmmunoreactive cells, which had increased after chemotherapy, decreased in the gastrointestinal mucosa after administration of DJT[13]. The antitumor agent cisplatin activates serotonin synthesis and inhibits monoamine oxidase (MAO), an enzyme that degrades serotonin. DJT normalizes MAO. Also, DJT increases gastrin, which accelerates gastric acid secretion[13]. Theoretically, this may be why DJT is effective in the treatment of CINV.

Pharmacopuncture can be used for patients who are reluctant to take herbal medicine orally. An additional advantage is that the administration of only a small amount shows a similar effect to the oral administration of the herbal medicine. In particular, intravenous pharmacopuncture is a method of injecting the processed herbal medicine directly into the blood vessels, which is faster than traditional pharmacopuncture. In China, many studies of intravenous pharmacopuncture have been conducted. However, the use of intravenous pharmacopuncture in Korea is limited to certain herbal medicines, primarily wild ginseng. Apart from wild ginseng studies, only two other intravenous pharmacopuncture studies (Gamisoyo-san and banhasasim-tang) exist[14]. We believe the present study provides important information and fills a gap in the literature.

Cisplatin, an anticancer drug, causes vomiting in 30% to 90% of patients[26]. Because rodents do not vomit directly, they exhibit a characteristic behavior of ingesting non-nutrients such as kaolin when stimulated with a vomiting agent such as cisplatin[27]. In rats, this behavior is known to be related to the gastrointestinal vagus nerve[28]. In rats injected with cisplatin, the intake of kaolin increases; therefore, kaolin is used as an indirect indicator of rat nausea and vomiting[29].

In the present study, cisplatin-induced nausea and vomiting responses were less in rats administered DJT. Also, 48 h after administration of cisplatin, the amount of residual food in stomachs was significantly higher in DJT groups than in the cisplatin group. It is thought that DJT reduces gastrointestinal tract obstruction. The result of this study indicates that DJT intravenous pharmacopuncture may be effective in CINV.

Among DJT-injected rats, the DJT-2 group (DJT concentration of 0.104 g/kg) had the smallest amount of residual food in the stomach. This group also showed the smallest kaolin intake (Fig. 9). Further studies are needed to determine why this concentration is most effective, and research into the most effective concentration for humans should be conducted.

V. Conclusions

In conclusion, DJT intravenous pharmacopuncture is likely to be effective for cisplatin-induced emesis and gastrointestinal mobility disorders. However, this study is limited to animals, and human studies are needed before the clinical applications can be confirmed. In addition, as DJT is a complex, multi-component prescription and not a simple one-herb medicine, research into the various components is needed. Furthermore, research into the specific mechanism of DJT intravenous pharmacopuncture and the comparison between intravenous pharmacopuncture and simple oral administration are needed.

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