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Original Article

Rotational intraperitoneal pressurized aerosol chemotherapy with paclitaxel and cisplatin: pharmacokinetics, tissue concentrations, and toxicities in a pig model

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ABSTRACT

Objective: We used paclitaxel and cisplatin, known to be effective in intraperitoneal chemotherapy, in a novel prototype of rotational intraperitoneal pressurized aerosol chemotherapy (RIPAC) and evaluated the pharmacokinetics, tissue concentrations, and toxicities in a pig model.

Methods: We developed RIPAC, including the nozzle with the conical pendulum motion, and used 10% of intravenous doses of paclitaxel and cisplatin. We used high-performance liquid chromatography followed by tandem mass spectrometry to analyze serum and tissue concentrations. We applied a non-compartment model to study pharmacokinetics to analyze the time-dependent serum concentrations measured before RIPAC to 48 hours. We evaluated the difference in tissue concentrations between twelve peritoneal regions by the modified peritoneal cancer index. For evaluating toxicities, we observed hepatic and renal function until 4 days after RIPAC.

Results: Six pigs underwent RIPAC using paclitaxel (n=3) and cisplatin (n=3). The peak serum concentration (C_{max}) and the area under the curve were higher for cisplatin, while the time to the peak serum concentration (T_{max}) was longer for paclitaxel. Moreover, the parietal peritoneum showed higher tissue concentrations than the visceral peritoneum, and the ratio of tissue to serum concentrations using C_{max} was higher for paclitaxel (172.2–6,237.9) than for cisplatin (0.1–9.3). However, there were no renal and hepatic toxicities after RIPAC with paclitaxel or cisplatin.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data Sharing Statement
The datasets generated during and/or analyzed during the current study are available at https://drive.google.com/drive/folders/14zbsdt-RWxda2heZDw4dMIvYGdCTujyt?usp=sharing.

Author Contributions
Conceptualization: K.H.S.; Data curation: P.S.J., L.E.J., S.A., P.S., H.J., L.W., K.H.S.; Formal analysis: P.S.J., L.E.J., Y.G.W., K.H.S.; Funding acquisition: K.H.S.; Investigation: P.S.J., L.E.J., S.A., H.J., Y.G.W., S.S.H., L.W., C.S.J., S.G., P.J.W., K.H.S.; Methodology: P.S.J., L.E.J., P.S., Y.G.W., S.S.H., L.W., C.S.J., S.G., P.J.W., K.H.S.; Project administration: K.H.S.; Resources: K.H.S.; Software: P.S.J.; Validation: P.S.J.; Writing - original draft: P.S.J., K.H.S.

Conclusion: Delayed absorption of paclitaxel sprayed by RIPAC into the peritoneum to the bloodstream may lead to higher tissue concentrations at different regions and lower serum concentrations than cisplatin.

Keywords: Aerosol; Paclitaxel; Cisplatin; Pharmacokinetics; Drug Delivery Systems; Peritoneal Neoplasms

Synopsis
- Rotational intraperitoneal pressurized aerosol chemotherapy (RIPAC) using paclitaxel and cisplatin is feasible without toxicity.
- Paclitaxel showed slower distribution to the tissue and blood, higher tissue concentration than cisplatin after RIPAC.
- On the other hand, paclitaxel showed lower serum concentration than cisplatin after RIPAC.

INTRODUCTION

Among solid tumors with peritoneal metastasis (PM), epithelial ovarian cancer (EOC) is diagnosed with advanced-stage disease in about 80% of patients because of no effective screening method and specific tumor biology, which leads to poor prognosis [1]. For improving the prognosis of EOC, optimal cytoreduction to no gross residual disease [2], targeted therapy using bevacizumab and poly (ADP-ribose) polymerase inhibitors [3-5], and intraperitoneal chemotherapy such as hyperthermic intraperitoneal chemotherapy (HIPEC), have been shown to improve survival in patients with EOC [6,7].

Especially, intraperitoneal chemotherapy can enhance drug delivery at the peritoneal surface and eliminate microscopic tumors more effectively than intravenous chemotherapy [7], and hyperthermia during HIPEC can increase the penetration of the agents and drug sensitivity by impairing DNA repair, inducing apoptosis, and promoting the denaturing of proteins [8,9]. However, insufficient cycles caused by complications such as catheter-related problems and renal and hepatic toxicities up to 20% hinder wide clinical use. Moreover, the effect of intraperitoneal chemotherapy is limited in recurrent EOC [10].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been reported to be effective and safe as a palliative treatment even in recurrent diseases [11,12]. With only 10% of doses of anti-cancer agents used in intravenous chemotherapy, administered in the form of an aerosol under normothermia and capnoperitoneum of 12 mm, PIPAC may deliver more diffusely with fewer systemic toxicities [13-15]. Nevertheless, PIPAC has not gain popularity, and only doxorubicin and cisplatin are mainly used in solid tumors irrespective of types [16].

In previous studies, we reported the development of rotational intraperitoneal pressurized aerosol chemotherapy (RIPAC) to improve drug delivery by rotating the nozzle [17,18]. RIPAC using the new nozzle, Dreampen® (Dreampac Corp., Wonju, Korea), enhanced drug distribution in the abdominal cavity, tissue concentration, and penetration depth of doxorubicin into the peritoneum compared with PIPAC in a pig model [19,20]. In this study, we report the pharmacokinetics, tissue concentrations, and toxicities when paclitaxel and cisplatin, the most effective drugs for treating ovarian cancer, were administered during RIPAC in a pig model.

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MATERIALS AND METHODS

1. RIPAC system

For delivering paclitaxel and cisplatin as aerosols, we used RIPAC, which sprayed about 30 μm droplets through the nozzle with a velocity of 5 km/h at the flow rate of 30 mL/min under the pressure of 7 bars (=101 psi) [18]. The mean diameter of the sprayed region by Dreampen® (Dreampac Corp., Wonju, Korea) was 18.5 cm, and the penetration depth ranged from 360 to 520 μm [18,20], which were comparable to the values from previous studies using the microinjector (Capnopen®; Capnomed, Villingendorf, Germany) [21,22].

Furthermore, we added the conical pendulum motion device for rotating the nozzle during RIPAC. The conical pendulum motion device consists of a DC motor (12V/1.5A, GM35A-3323; Motorbank, Seoul, Korea), a 3D printed rotational stick, 2 end-stops (PCB mounted End-stop switch, RepRap, England), and an Arduino Uno. We inserted Dreampen® (Dreampac Corp.) in a 3D printed rotational stick and locked it with a screw. The angle between the nozzle and the vertical line was determined at 30 degrees by considering the spraying angle of about 70 degrees. The rotational stick rotated only in the same direction because the tube connected between the nozzle and the syringe pump could be tangled. Thus, the rotational stick moved clockwise, and when the sensor attached to the rotating stick contacted the rod of the rotating path, it moved counterclockwise to maintain repetitive rotation (**Fig. 1**; **Video S1**) [17,19].

2. Reagents

We purchased cis-diammineplatinum (II) dichloride (cisplatin) from Sigma-Aldrich (St. Louis, MO, USA), and paclitaxel was donated from Samyang Biopharmaceuticals Corp. (Seongnam, Korea). For analyzing serum and tissue concentrations of paclitaxel and cisplatin, we purchased acetonitrile and methanol from Fisher Scientific (Waltham, MA,

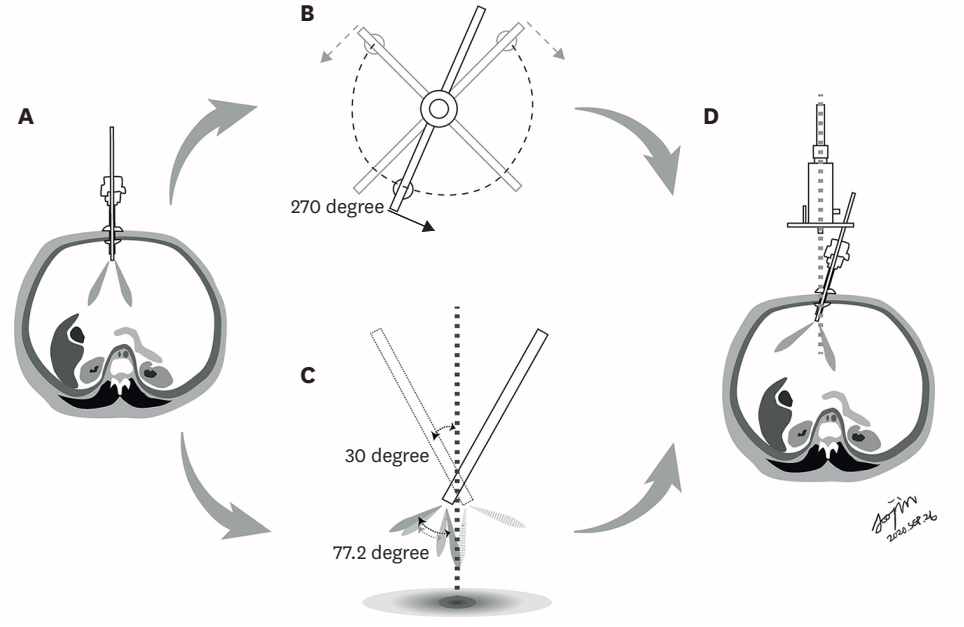

Fig. 1. Development process of RIPAC: (A) development of a novel prototype for pressurized intraperitoneal aerosol chemotherapy; (B) addition of the conical pendulum motion device for rotating the nozzle; (C) the developed nozzle with the spraying angle of about 70 degrees; and (D) the final prototype for RIPAC using the developed nozzle rotated by the conical pendulum motion device.
RIPAC, rotational intraperitoneal pressurized aerosol chemotherapy.

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USA) and formic acid, acetic acid, ammonium diethyldithiocarbamate, and ammonium acetate from Sigma-Aldrich.

3. Preparation

The Institutional Animal Care and Use Committee of Seoul National University Hospital approved this study in advance (No. 18-0051-S1A0). We bought a total of 6 female pigs weighing 40 to 50 kg for this study, and 2 groups of 3 pigs were used to assess the pharmacokinetics, tissue concentrations, and toxicities after RIPAC, with each group assigned to paclitaxel (n=3) and cisplatin (n=3).

Before RIPAC, we applied capnoperitoneum by CO_2 insufflation via a Veress needle to each pig. Then we inserted 2 or 3 12 mm bladeless trocars (Eagleport®; Dalim Medical Corp., Seoul, Korea) along the midline of the abdomen, which was used as passages for inserting the nebulizer and laparoscopic devices (Stryker Korea Co., Ltd., Seoul, Korea). For determining the equivalent doses for RIPAC in pigs, 25 mg/m^2 of paclitaxel and 7.5 mg/m^2 of cisplatin, which was about 10% dose used in intravenous chemotherapy for humans, were converted to 0.57 mg/kg of paclitaxel and 0.21 mg/kg of cisplatin [23]. After putting the nozzle through the trocar directly down to the ileum, RIPAC was conducted using each 0.57 mg/kg of paclitaxel and 0.21 mg/kg of cisplatin in 0.9% NaCl of 50 mL for evaluating the pharmacokinetics, tissue concentrations, and toxicities in the 2 groups.

4. Analysis of pharmacokinetics and toxicities

For evaluating the pharmacokinetics of paclitaxel and cisplatin, we obtained serum samples from the 2 groups at eleven times as follows: before RIPAC; after 15 minutes; after 30 minutes; after 45 minutes; after 60 minutes; after 75 minutes; after 90 minutes; after 105 minutes; after 120 minutes; after 24 hours; and after 48 hours. For calculating serum concentrations of paclitaxel, we mixed 200 μL of the serum with 50 μL of the internal standard solution (docetaxel, 2,000 ng/mL in 50% mannitol). Then, we added 1.7 mL of acetonitrile to the mixture and vortexed it for 5 minutes. After 2 minutes of centrifuge at 4,000 rpm, the supernatant was dried in SpeedVac for 140 minutes at 45°C. The sample was reconstituted to 100 μL of the mixture of 5 mM ammonium acetate and 0.1% acetic acid acetonitrile with a ratio of 50:50 and vortexed for 20 seconds. The mixture was aliquoted to 15 μL of the volume for injection.

For estimating the serum concentration of cisplatin, we mixed 50 μL of the serum with 15 μL of 2% diethyldithiocarbamate solution and incubated it in the heating block at 40°C for 30 minutes. Then, 1.5 mL of the internal standard solution (carbamazepine, 0.1 ng/mL in acetonitrile) was mixed and centrifuged at 13,000 rpm for 5 minutes. The supernatant was dried in SpeedVac for 90 minutes at 45°C and reconstituted to 100 μL of the mixture of distilled water, acetonitrile, and formic acid with the ratio of 80:20:0.1. Then, the mixture was transferred and injected 5 μL for analysis.

For investigating renal and hepatic toxicities, we collected serums of the same 6 pigs a total of 6 times as follows: before RIPAC, immediately after RIPAC, after one to 4 days after RIPAC. Then, we calculated serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), bilirubin, alkaline phosphatase (ALP), creatinine, and C-reactive protein (CRP).

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5. Analysis of tissue concentrations

To assess tissue concentrations in specific regions of the abdominal cavity, we modified the peritoneal cancer index (PCI) [24] and obtained tissues from 9 regions of the parietal peritoneum (central, right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, and right flank) and 3 regions of the visceral peritoneum (ileum, jejunum, and stomach) according to the modified PCI (**Fig. S1**). Based on the modified PCI, we obtained 2×2 cm sized peritoneal tissue samples from all regions of the 6 pigs after RIPAC and stored them at −80°C. The peritoneal tissue sample was homogenized with 1 mL of acetonitrile and vortexed for 30 minutes. After staying overnight in the refrigerator, the sample was centrifuged at 14,000 rpm for ten minutes. The supernatant was then dried in SpeedVac for 180 minutes at 45°C, and the dried sample was reconstituted to 50 μL volume.

For analyzing tissue concentration of paclitaxel, the sample was mixed with 50 μL of the internal standard solution (docetaxel, 2,500 ng/mL in acetonitrile). After we vortexed it for 30 seconds, the sample was centrifuged, and the supernatant was transferred and divided into 5 μL of the volume for injection. For evaluating tissue concentration of cisplatin, the sample was mixed with 15 μL of 2% diethyldithiocarbamate solution. The mixture was incubated at 40°C, and 1.5 mL of the internal standard solution (carbamazepine, 0.1 mg/mL in acetonitrile) was added. After centrifuged, the supernatant was dried again in SpeedVac for 90 minutes at 45°C and reconstituted to 100 μL of the mixture of distilled water, acetonitrile, and formic acid with the ratio of 80:20:0.1. The mixed sample was mixed and divided into 5 μL of aliquots for injection.

6. Liquid chromatography and tandem mass spectrometry

High-performance liquid chromatography (HPLC) using Agilent 1260 infinity (Agilent, Santa Clara, CA, USA) and tandem mass spectrometry (MS/MS) using API4000QTRAP (Applied Biosystems, Foster City, CA, USA) were used for analyzing serum and tissue concentrations of paclitaxel and cisplatin. Gemini 5 μm C18, 50×2.0 mm (Phenomenex, Torrance, CA, USA) was used as the analytical column during HPLC. For analyzing paclitaxel concentrations, 5 mM ammonium acetate and 0.1% acetic acid acetonitrile were used as the mobile phase with the flow rate of 0.3 mL/min over 6.5 minutes under the temperature of 25°C. For analyzing cisplatin concentrations, the mobile phase composed of 0.1% formic acid with distilled water and acetonitrile with the flow rate of 0.35 mL/min over 9 minutes at 25°C was used during HPLC.

The scan type of MS/MS, which was equipped with positive ionization mode (Turbo Spray), was the multiple reaction monitoring for quantification. The pressure of the nebulizer and desolvation gas was 50 psi, both composed of nitrogen. MS/MS was regulated under the needle voltage at 5,000 V, and the set temperature was 400°C for paclitaxel and 350°C for cisplatin analysis. The acquisition delay was 0 second, and the pause time was 5 msec.

7. Statistical analysis

We performed the pharmacokinetics study for RIPAC with paclitaxel and cisplatin, based on a non-compartment model using the R software for pharmacokinetic analysis. For the characterization of pharmacokinetic analysis, the peak serum concentration (C_{max}, ng/mL) and the time measurement to the peak serum concentration (T_{max}, hour) were identified. Then, the area under the curve (AUC, ng/mL*hour) of the individual pharmacokinetic curve was calculated using the linear trapezoidal rule from zero to the time of the last observed positive concentration. The other analysis was conducted with SPSS 22.0 (IBM, Armonk, NY, USA), and all p-values were considered significant if less than 0.05.

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RESULTS

Time-dependent serum concentrations were depicted in **Table S1**, and the pharmacokinetic properties of paclitaxel and cisplatin used in RIPAC were shown in **Fig. 2**. Mean values of C_{max} and AUC after RIPAC were higher for cisplatin than for paclitaxel (C_{max}, 187.6 vs. 4.68 ng/mL; AUC, 164.23 vs. 7,851.41 ng/mL). On the other hand, the mean values of T_{max} after RIPAC was longer for paclitaxel than for cisplatin (24 vs. 2 hours; **Table 1**).

Tissue concentrations after RIPAC, according to the modified PCI, are shown in **Table S2**. Maximal mean values of tissue concentrations were observed in the left upper region for paclitaxel (75,993.33 ng/mL) and the pelvis and right lower regions for cisplatin (1,484.67 and 1,751.03 ng/mL). Although tissue concentrations of paclitaxel and cisplatin were different among different regions of the parietal peritoneum, their tissue concentrations showed the

Table 1. Pharmacokinetic variables for rotational intraperitoneal pressurized aerosol chemotherapy with paclitaxel and cisplatin in a pig model

Variables	Paclitaxel (0.57 mg/kg)			Cisplatin (0.21 mg/kg)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
C_{max} (ng/mL)	4.68	0.12	0.02	187.60	24.38	0.13
AUC* (ng/mL)	163.23	9.94	0.06	7,851.41	1,047.65	0.13
T_{max} (hr)	24	0	0	2	12.70	1.36

AUC, area under the curve; C_{max}, peak serum concentration; CV, coefficient of variation; SD, standard deviation; T_{max}, time measurement to C_{max}.
*AUC was calculated from the time zero to the time of the last positive concentrations.

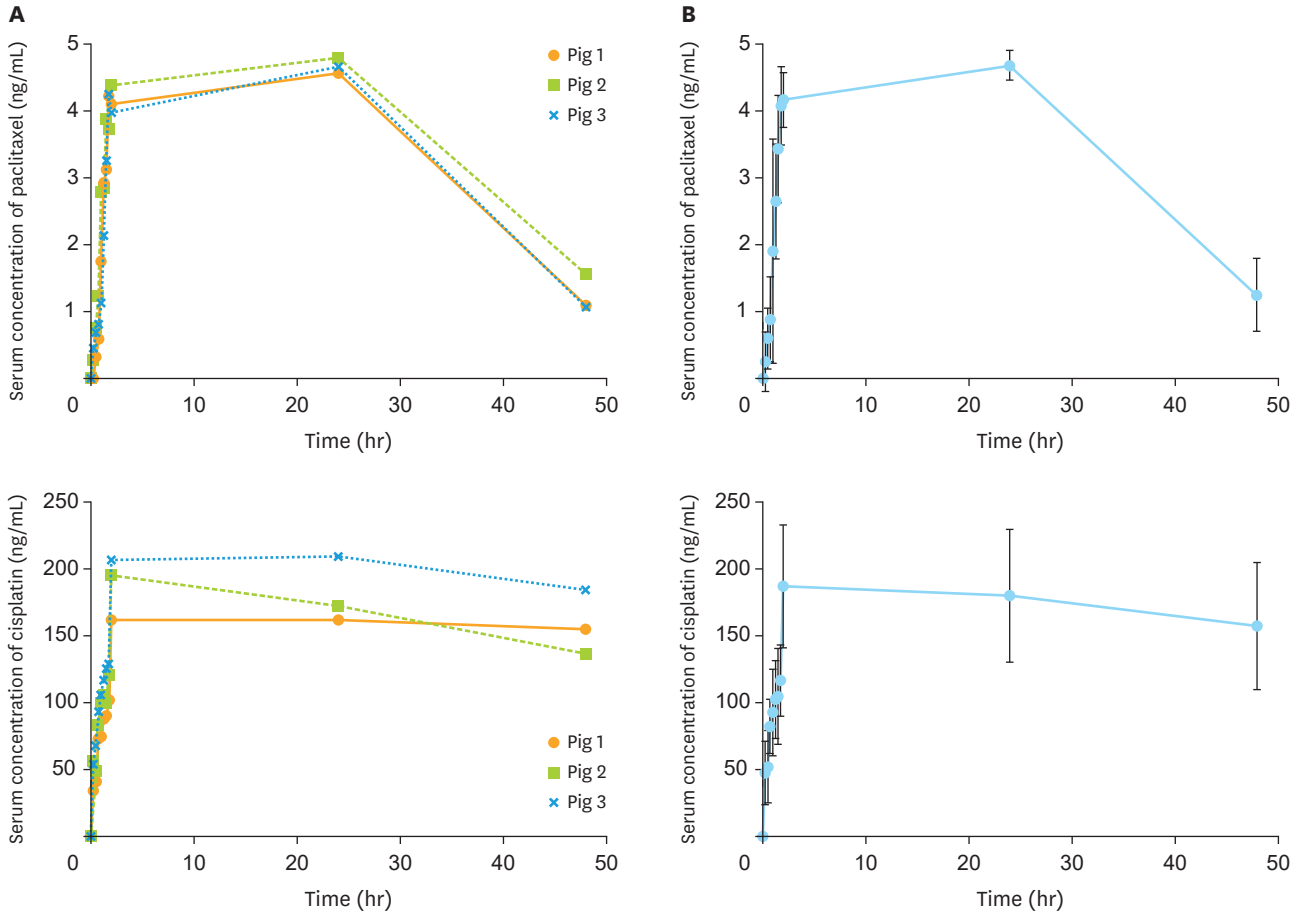

Fig. 2. Time-dependent serum concentrations of paclitaxel and cisplatin used in rotational intraperitoneal pressurized aerosol chemotherapy. Data are shown for individuals (A) and groups (B).

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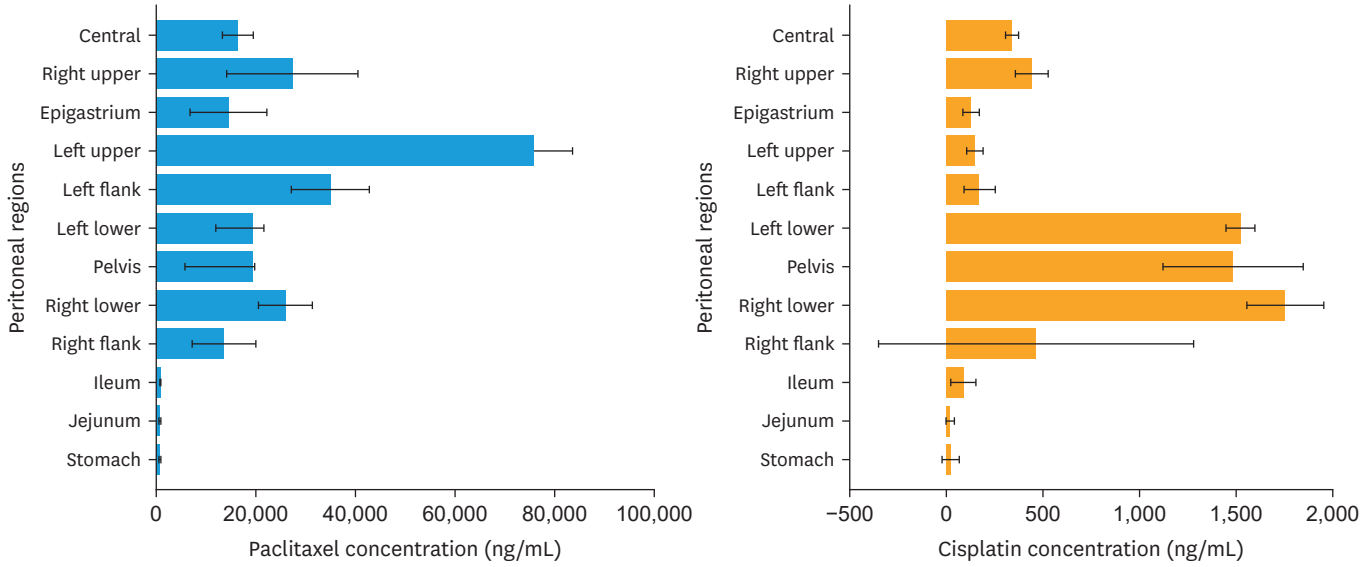

Fig. 3. Tissue concentrations of paclitaxel and cisplatin used in rotational intraperitoneal pressurized aerosol chemotherapy according to the modified peritoneal cancer index.

tendency to be higher than those in the ileum, jejunum, and stomach regions of the visceral peritoneum (mean values; paclitaxel, 12,870.67–75,993.33 ng/mL vs. 808.43–889.13 ng/mL; cisplatin, 350.54–1,751.03 ng/mL vs. 19.87–88.843 ng/mL; **Fig. 3**).

Mean values of tissue concentrations of paclitaxel were higher than those of cisplatin, showing that tissue concentrations of paclitaxel reached 2.2 to 3,883.2 times those of cisplatin. Furthermore, the ratio of tissue to serum concentrations using C_{max} ranged from 172.2 to 6,237.9 for paclitaxel and from 0.1 to 9.3 for cisplatin.

Table 2 shows renal and hepatic toxicities before and after RIPAC with paclitaxel and cisplatin. As a result, there were no differences in creatinine, bilirubin, ALP, AST, ALT, GGT, and CRP before RIPAC, immediately after RIPAC, Day 1, Day 2, Day 3, and Day 4.

Table 2. Comparison of toxicities related to RIPAC with paclitaxel and cisplatin in a pig model

Parameters	Measurement time						
	Before RIPAC	Immediately after RIPAC	Day 1	Day 2	Day 3	Day 4	p-value
Paclitaxel							
Creatinine (mg/dL)	1.08±0.29	1.20±0.39	1.25±0.26	1.09±0.29	1.14±0.26	1.17±0.26	0.82
Bilirubin (mg/dL)	0.15	0.15	0.15	0.15	0.15	0.15	1.00
ALP (IU/L)	116.33±25.69	110.01±30.01	124.67±8.51	95.33±11.59	93.67±13.42	95.33±14.74	0.27
AST (IU/L)	22.33±6.43	18.33±3.06	32.01±11.13	15.67±8.51	24.67±15.57	17.67±3.51	0.44
ALT (IU/L)	30.67±4.04	31.67±4.16	42.21±13.45	32.33±9.45	34.33±11.85	37.33±16.29	0.74
GGT (IU/L)	50.67±3.51	43.67±2.89	49.01±5.29	42.33±4.62	48.12±1.01	43.67±10.21	0.20
CRP (g/L)	0.10	0.10	0.10	0.10	0.10	0.10	1.00
Cisplatin							
Creatinine (mg/dL)	1.11±0.13	1.02±0.21	1.12±0.12	1.07±0.15	1.01±0.24	1.10±0.18	0.99
Bilirubin (mg/dL)	0.15	0.15	0.15	0.15	0.15	0.15	1.00
ALP (IU/L)	127.33±14.05	122.01±18.03	134.33±17.62	116.33±18.77	111.67±18.58	105.67±15.04	0.31
AST (IU/L)	24.01±6.01	28.67±12.66	27.01±5.20	16.67±2.52	39.01±38.97	16.33±4.16	0.32
ALT (IU/L)	31.33±4.04	31.66±3.06	34.33±3.06	31.33±4.04	33.67±3.21	29.33±4.04	0.49
GGT (IU/L)	42.67±10.41	36.33±2.08	38.01±7.55	36.33±8.03	38.01±8.54	35.67±6.51	0.83
CRP (g/L)	0.10	0.10	0.10	0.10	0.10	0.10	1.00

All values were shown as mean ± standard deviation.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; RIPAC, rotational intraperitoneal pressurized aerosol chemotherapy.

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DISCUSSION

After we developed RIPAC as a novel prototype of PIPAC for improving drug delivery, we tried to evaluate the effect and safety of RIPAC for treating EOC with PM [17-20]. In the previous report, we compared the distribution, tissue concentration, and diffusion of doxorubicin between PIPAC and RIPAC, suggesting that RIPAC may have the potential to enhance drug delivery into the peritoneum compared to PIPAC [19]. Since paclitaxel and cisplatin were the main agents for intraperitoneal chemotherapy that have been shown to improve survival in the Gynecologic Oncology Group (GOG)-172 and HIPEC trials for advanced ovarian cancer [6,7], we further investigated the pharmacokinetics, tissue concentrations, and toxicities of RIPAC with paclitaxel and cisplatin in this study.

Considering the pharmacokinetic properties of paclitaxel and cisplatin in RIPAC, we found that cisplatin reached a higher level of the peak serum concentration faster than paclitaxel. A few relevant studies reported that mean values of C_{max} were higher for cisplatin after PIPAC (121 ng/mL) than for paclitaxel (14.6 ng/mL), and the mean value of T_{max} for paclitaxel was 4 hours, similar to the result from this study [25,26]. These findings can be supported by the molecular characteristics that cisplatin is hydrophilic and has a relatively low molecular weight of 301.1 g/mol, whereas paclitaxel is hydrophobic and has a relatively high molecular weight of 853.91 g/mol [27,28]. The differences may lead cisplatin to be absorbed faster into the peritoneum and the blood circulation than paclitaxel.

On the other hand, we found that tissue concentrations of paclitaxel were 2.2 to 3,883.2 times higher than those of cisplatin after RIPAC. This finding suggests that delayed absorption of paclitaxel into the peritoneum might delay the distribution into the blood circulation and result in a cumulative increase in tissue concentrations. A previous study where paclitaxel persisted in the peritoneum for one week after intraperitoneal administration also supports this finding, suggesting that the peritoneal clearance of paclitaxel might be slow and relevant toxicities might be increased due to the prolonged detection of paclitaxel [29].

Moreover, we thought that paclitaxel might be more beneficial than cisplatin in terms of the ratio of tissue to serum concentrations because it was higher for paclitaxel than for cisplatin (172.2–6,237.9 vs. 0.1–9.3). Previous studies also reported that ratios of tissue to serum concentrations were about 200 for doxorubicin [11,14], and 2 to 44.3 for oxaliplatin after PIPAC [30]. Consequently, paclitaxel can be suggested as the most appropriate agent in terms of the ratio of tissue to serum concentrations due to lower serum levels to reduce toxicities and to maximize tissue concentrations.

However, there were no renal and hepatic toxicities after RIPAC in this study. Relevant studies also showed a similar safety profile after PIPAC [14,31,32], which implies that about 10% dose of intravenous chemotherapy may be safe after PIPAC or RIPAC. Nevertheless, the safety of RIPAC using low doses of paclitaxel and cisplatin require further investigations because the presence of synergic toxicities while combining drugs has been suggested for patients treated with intraperitoneal chemotherapy [16,33].

Interestingly, tissue concentrations were higher in other regions than the ileum region directly opposite the nozzle. A previous study reported that the penetration of doxorubicin was highest in the small intestine directly opposite and around the nozzle, whereas it was minimal in other regions in the abdominal cavity [34]. Even though the ileum region was

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located not only direct to the nozzle but also in the center of the overlapping area sprayed from the rotating nozzle, we found that the tissue concentration of paclitaxel and cisplatin after RIPAC were relatively higher in regions other than the ileum region, unlike PIPAC. Considering the same flow rate of 30 mL/min and the similar diameter of aerosol between PIPAC and RIPAC, RIPAC is expected to show the lower velocity of aerosol and the larger injection outlet, reducing the turbulent flow of aerosol and prolonging breakup-length within the sprayed zone. Moreover, subsequent increase of deflection may lead to increased movement of aerosol in wider regions of the peritoneum [20].

Especially, tissue concentrations in the visceral peritoneum, including the ileum, were lower than in the parietal peritoneum. Thus, we postulated that differences in histologic structure between the visceral and parietal peritoneum rather than the nozzle position could lead to these uneven concentrations. In general, the peritoneum thickness is known to range from 100 to 200 μm [35]. When we consider that the penetration depth of RIPAC may range from 360 to 520 μm, it may exceed the thickness of the peritoneum [17]. The agents sprayed in the form of aerosol under high pressure can penetrate the soft extraperitoneal fat tissues beyond the parietal peritoneum, whereas it seems that it will be difficult to diffuse into the hard muscularis layer beyond the visceral peritoneum [36,37]. Our previous study supported this hypothesis where mean values of tissue concentrations were also lower in the visceral peritoneum than in the parietal peritoneum after RIPAC with doxorubicin [19].

This study has some limitations as follows: first, serum and tissue concentrations with various doses of paclitaxel and cisplatin were not evaluated using a larger number of pigs for obtaining more precise results; second, the interpretation of tissue concentrations should be based on the penetration depth, not conducted in this study; third, the actual effect of paclitaxel should be proved through basic experiments even though paclitaxel appeared to be the most suitable in terms of the ratio of tissue to serum concentrations; fourth, the effect of RIPAC, which might have superior drug delivery ability than PIPAC, should be proven through preclinical and clinical trials. Especially, tumors on the peritoneum and tissue adhesion can act as a bias to evaluate pharmacokinetics and tissue concentration of agents used for treating ovarian cancer. So, we developed a pig model with PM (patent No. 10-2019-01100793, Korea; No. 16846321, USA), and will conduct similar studies for this model, considering basic results of this study not affected by tumor location and adhesion. Furthermore, prospective cohort studies for evaluating feasibility of RIPAC, phase II and III trials will be conducted sequentially for patients with ovarian and colon cancers with the support of Dreampac Corp. and Precision Medicine for Peritoneal Metastasis Corp. (Wonju, Korea) from this year in Korea.

In conclusion, RIPAC using paclitaxel and cisplatin may be expected to be safe with fewer systemic toxicities. Moreover, delayed absorption of paclitaxel into the peritoneum and to the bloodstream is expected to be more beneficial than cisplatin because paclitaxel may lead to higher tissue concentrations at different peritoneal regions and lower serum concentrations, compared to cisplatin.

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SUPPLEMENTARY MATERIALS

Table S1

Comparison of serum concentrations of paclitaxel and cisplatin used in rotational intraperitoneal pressurized aerosol chemotherapy

Click here to view

Table S2

Comparison of tissue concentrations of paclitaxel and cisplatin used in rotational intraperitoneal pressurized aerosol chemotherapy

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Fig. S1

The modified peritoneal cancer index scoring system.

Click here to view

Video S1

Video motion showing clockwise and counterclockwise rotation during rotational intraperitoneal pressurized aerosol chemotherapy in a pig model.

Click here to view

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