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Ideal Nozzle Position During Pressurized Intraperitoneal Aerosol Chemotherapy in an *Ex Vivo* Model

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Abstract. *Background/Aim: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is known to show uneven distribution and penetration of agents based on the nozzle position. Thus, this study aimed to investigate the ideal nozzle position for maximizing drug delivery during PIPAC. Materials and Methods: We created 2 cm-, 4 cm- and 8 cm-ex vivo models according to the distance from the bottom to the nozzle using 21×15×16 cm-sized sealable plastic boxes. After each set of eight normal peritoneal tissues from swine were placed at eight different points (A to H), we performed PIPAC, compared the methylene blue staining areas to investigate the distribution, and estimated the depth of concentrated diffusion (DCD) and the depth of maximal diffusion (DMD) of doxorubicin. Results: In terms of distribution, the 4 cm- and 8 cm-ex vivo models showed more stained faces than the 2 cm-ex vivo model. Regarding the penetration depth, the 4 cm- ex vivo model showed the highest DCD (mean; 244.1 μm, C; 105.1 μm, D; 80.9 μm, E; 250.2 μm, G; 250.2 μm, H) and DMD (mean; 174.8 μm, D; 162.7 μm, E; 511.7 μm, F; 522.2 μm, G; 528.1 μm, H) in the most points corresponding to 62.5%. Conclusion: The ideal nozzle position during PIPAC might be halfway between the nozzle inlet and the bottom in the ex vivo model.*

Peritoneal metastasis (PM) commonly occurs in advanced or recurrent diseases of solid tumors and is found in up to 60-70% of patients with gastric, colorectal, and ovarian cancers (1-3). However, effective methods for treating PM are limited, therefore its prognosis is still poor despite intravenous chemotherapy (IV), and targeted- or immuno-oncologic treatment does not yet have a breakthrough therapeutic effect in patients with PM.

For improving tumor response and survival of patients, intraperitoneal chemotherapy (IP) has been introduced in clinical settings, and the combination of IP followed by cytoreductive surgery (CRS) and IV has been suggested to have the potential to be more effective than IV alone for gastric, colorectal, and ovarian cancer patients by resulting in longer progression-free and overall survivals (4-6). However, the burden of CRS and reduced cycles due to increased IP toxicity still limit the general use of IP for treating PM (7).

Alternatively, hyperthermic intraperitoneal chemotherapy (HIPEC) is used because hyperthermia of 41-43˚C may

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contribute to destroying the microtubule system, inducing protein degeneration, and inhibiting angiogenesis in tumors (8, 9). Based on this potential, HIPEC has been suggested to improve survival compared to IV alone for patients with advanced or recurrent ovarian cancer who underwent CRS (10, 11). Nevertheless, grade 3 or 4 renal or hepatic toxicities of up to 20% and only one application immediately after CRS limit the clinical use of HIPEC (11).

Recently, pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been used for the palliative treatment of patients with PM that limits the side effects of conventional IP in some European countries and Singapore (12-14). PIPAC delivers 10% of agents used in IV as an aerosol into the abdominal cavity (15), and the tissue concentration is known to reach up to 200-times higher after PIPAC than after IP because of the increased penetration depth of agents by a high-pressure injector in a 12 mmHg-pressurized capnoperitoneum (16). On the other hand, the toxicities related to PIPAC are minimal compared to IV or IP due to lower plasma levels of agents (17). Thus, these features have contributed to the use of PIPAC as palliative treatment for refractory solid tumors with PM.

However, PIPAC has a major limitation of uneven drug delivery into the peritoneum because agents are not distributed and penetrated properly in the other areas except for the opposite side of the nozzle used in PIPAC (18-20). When we consider that the structure of the human body cavity is different for each woman, there is still a lack of evidence about which position of the nozzle used in PIPAC, CapnoPen® (Capnomed, Villingendorf, Germany), may be able to maximize drug delivery into all target regions, and how the penetration of agents sprayed into different regions of the abdominal cavity may change according to its various positions.

Thus, we aimed to investigate the ideal nozzle position that can maximize the drug distribution and penetration, including the depth of concentrated depth (DCD) and the depth of maximal diffusion (DMD) during PIPAC in an *ex vivo* model by using the new nozzle we developed previously, DreamPen® (Dalim Medical Corp., Seoul, Republic of Korea) (21).

Materials and Methods

Ex vivo model. We created an *ex vivo* model for PIPAC using a sealable plastic box reproducing the asymmetrical human body cavity. The width, depth, and height were measured 21, 15, and 16 cm, respectively, with a total volume of 3.5 l. The plastic box was placed in a water bath at a constant temperature of 36˚C during the entire procedure. On the top of the plastic box, two 12 mm trocars (Eagle-port®, Dalim Medical Corp., Seoul, Republic of Korea) were placed at 7-cm intervals. Using the two trocars, DreamPen® (Dalim Medical Corp., Seoul, Republic of Korea) was inserted for delivering agents as an aerosol, and a temperature sensor was connected.

A total of 24 peritoneal tissue specimens (3×3×0.5 cm) were obtained from fresh postmortem swine weighing 50 kg for making 2 cm-, 4 cm-, and 8 cm- *ex vivo* models where the distance from the bottom to the nozzle was 2, 4, and 8 cm, respectively. Each eight-tissue specimen was placed at eight different points in each *ex vivo* model, and it was pinned to its original size on a plate located at each point immediately after we obtained it from the fresh postmortem swine.

The nozzle position and spatial location of each tissue (points A to H) were determined considering the asymmetrical abdominal cavity of the human body, and specifically, points A, B, C, D, E, F, G, and H reflected visceral organs located opposite the nozzle, the pelvis, the anterior abdominal peritoneum, the epigastrium, the diaphragm, visceral organs hidden by tumors or adhesions, the left flank, and the right flank, respectively (Figure 1).

PIPAC system. Since the current PIPAC delivery system did not exist in South Korea, we developed a novel prototype of PIPAC by using our medical engineering technology (Figure 2), and DreamPen® in this prototype was used to evaluate the ideal nozzle position during PIPAC (21). In short, this prototype sprayed about 30-um drug droplets through the nozzle with a velocity of 5 km/h at the flow rate of 30 ml/min with a pressure of 7 bars (=101 psi). The diameter of the sprayed region was 18.5±1.2 cm, and the penetration depth ranged from 360 to 520 μm, which were comparable to the values shown in previous studies (Table I) (12, 18-22).

To perform PIPAC, we sealed the plastic box tightly, and a capnoperitoneum of 12 mmHg was applied during this experiment by a laparoscopic system (KARL STORZ Endoscopy Korea CO., Ltd., Seoul, Republic of Korea). Then, we conducted PIPAC using 50 ml of 1% methylene blue (Sigma-Aldrich Inc., Seoul, Republic of Korea) to investigate the distribution in the three *ex vivo* models. We aerosolized 1% methylene blue solution with a flow rate of 30 ml/min. To evaluate the penetration depth according to the different distances from the bottom to the nozzle, we conducted PIPAC using 3 mg of doxorubicin (Sigma-Aldrich Inc.) in 50 ml of NaCl 0.9% because doxorubicin is known to be the most common agent used in PIPAC for treating PM regardless of types of solid tumors (13), and it has been most frequently used to assess the penetration depth by PIPAC (15, 17-19). During PIPAC, doxorubicin was also sprayed at a flow rate of 30 ml/min. After these procedures, we maintained a capnoperitoneum of 12 mmHg for 30 min, and then the aerosols were removed through a suction line connected by a trocar to an air-waste system equipped with a glass microfiber filter impregnated with a carbon layer (Laparo Clear Smoke Filtration Kit, pore size 0.027 um, diameter 50 nm, GVS Inc., Rome, Italy). The experiments were conducted three times for each *ex vivo* model.

Distribution and penetration depth. To investigate the distribution of 1% methylene blue, we compared the stained areas on the six faces in the three *ex vivo* models with the naked eye. To evaluate the penetration depth of doxorubicin, we rinsed all tissue specimens with 0.9% NaCl solution to remove doxorubicin on the surface and then froze them in liquid nitrogen immediately after mounting them by using optimal cutting temperature compound for eliminating tissue shrinkage and undesirable background staining. Thereafter, we prepared cryosections with a thickness of 7μm from three different areas of each specimen and applied 1.5 μg/ml of 4',6-diamidino-2-phenylindole (DAPI) (Sigma-Aldrich Inc.). We evaluated the penetration depth of doxorubicin at points A to H by confocal laser scanning microscopy (Leica TCS SP8) and compared it between the three *ex vivo* models. In this study, we evaluated the penetration depth of doxorubicin by using DCD estimated as the distance between the luminal surface and the surface where the

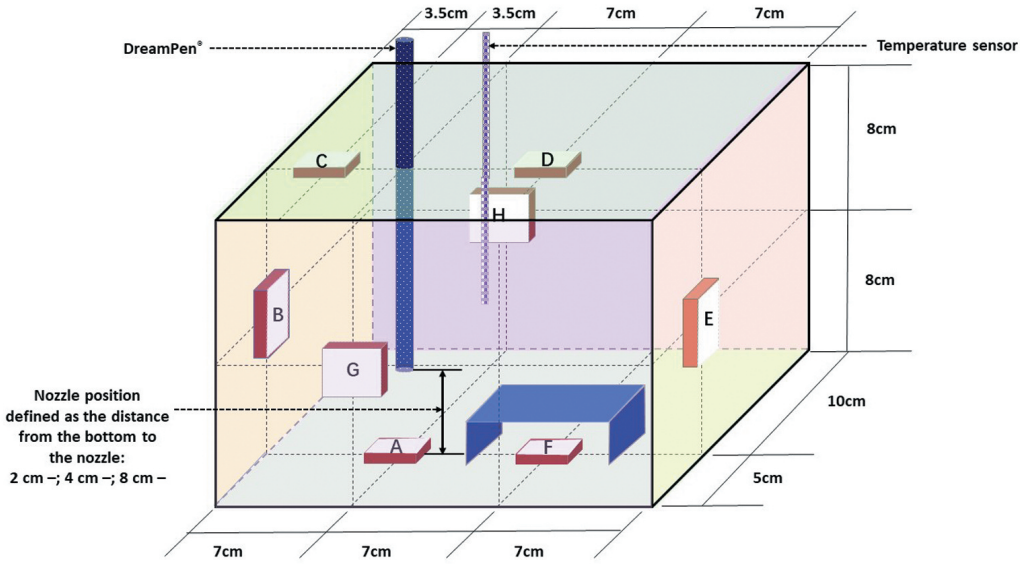


Figure 1. *The ex vivo model using a 21×15×16 cm sealable plastic box for pressurized intraperitoneal aerosol chemotherapy. Eight tissue specimens from fresh postmortem swine were fixed at points A to H determined by considering the asymmetrical abdominal cavity of the human body. Points A and F on the bottom face were located at one-third of the entire width and at one-third of the entire depth. Specifically, point A was placed on the bottom in the direct extension of the nozzle, and point F was placed on the inner side of the barrier where both sides were open. Point B on the left side face and point E on the right side face was located in the middle of the entire height, and at one-third of the entire depth along the same line as point A and F. Point D on the top face was placed opposite point F, and point C on the top face was located 3.5 cm away from the nozzle in the direction opposite from point D. Point G on the front face and point H on the back face were located at one-third of the entire width near point A, and in the middle of the entire height. The distance between the nozzle and the bottom was set to 2, 4, and 8 cm in the three ex vivo models to compare the penetration depth of doxorubicin and the distribution of 1% methylene blue.*

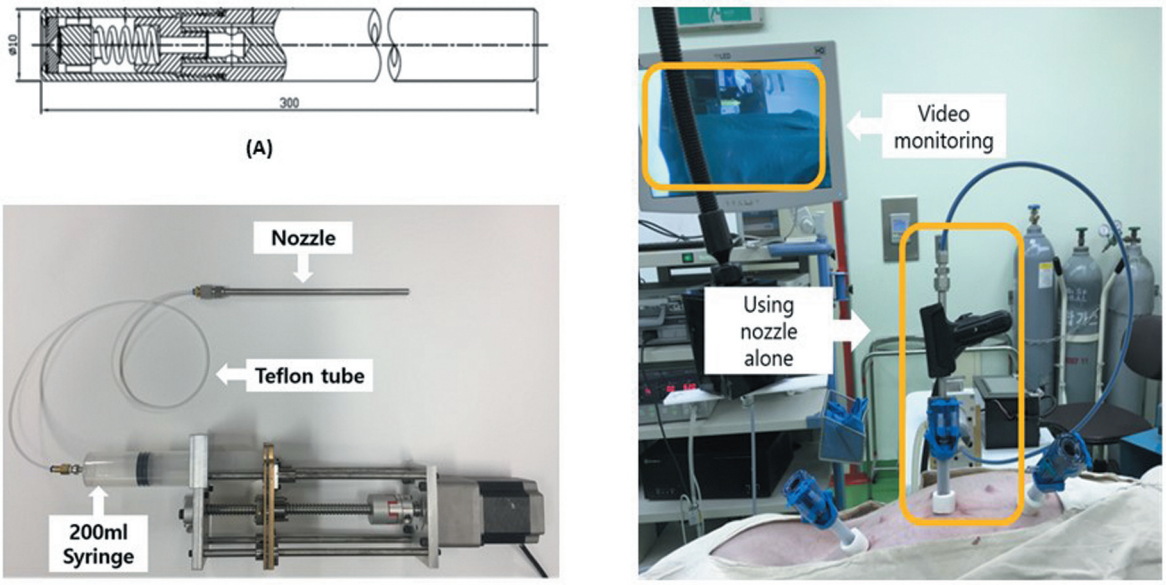


Figure 2. *A novel prototype for pressurized intraperitoneal aerosol chemotherapy (PIPAC): (A) the nozzle used in PIPAC (DreamPen®); (B) the new PIPAC system with DreamPen® connected to a 200 ml syringe; (C) preclinical application of the new PIPAC system.*

Table I. *Comparison of the performance between CapnoPen® and DreamPen®.*

Performance	CapnoPen®	DreamPen®
Injection velocity (km/h)	60	5
Relative size of injection outlet	Small	Large
Injection pressure (psi)	200	101
Flow rate (ml/min)	30	30
Median diameter of aerosol (um)	25	30
Diameter of the sprayed region (median, cm)	15	18.5
Depth of maximal diffusion in 2 cm- ex vivo models (median, μm)	469	515

positive doxorubicin staining was most accumulated, and DMD calculated as the distance between the luminal surface and the innermost depth at which positive doxorubicin staining could be visualized.

Statistical analysis. Statistical analyses were performed using the SPSS version 22 software (IBM Corp., Armonk, NY, USA), and the data were analyzed by the Kruskal-Wallis test and Mann-Whitney *U*-test with Bonferroni correction. In this study, a significant *p*-value was defined as $p<0.05$.

Results

Distribution. When we compared the stained areas on the six faces between the three *ex vivo* models, the bottom face was mainly stained in the 2 cm- *ex vivo* model. In the 4 cm- *ex vivo* model, the bottom face was strongly stained, and the side, front, back, and top faces were weakly stained. In the 8 cm- *ex vivo* model, the bottom, side, front, and back faces were strongly stained, and the top face was moderately stained, suggesting that the distribution range was wider in the 4 cm- and 8 cm- *ex vivo* models than the 2 cm- *ex vivo* model (Figure 3).

Penetration depth. Figure 4 shows the results of microscopic confocal laser analysis for evaluating DCD and DMD after PIPAC at points A to H in the three *ex vivo* models. When we compared DCD and DMD of each position subjectively between the three *ex vivo* models, DCD tended to increase with increasing distance between the nozzle and the bottom at points C, D, and F, whereas it tended to decrease with decreasing distance between the nozzle and the bottom at point H. Moreover, DMD tended to increase with increasing distance between the nozzle and the bottom at points B, C, D, F, and G, whereas it tended to decrease with decreasing distance between the nozzle and the bottom at points A, E, and H.

When we compared the differences in DCD and DMD, there were no differences in DCD among different distances at points A and B. In contrast, DCD was the highest at points C, D, and G in the 4 cm- and 8 cm- *ex vivo* models, whereas it was the highest at points E and H in the 2 cm- and 4 cm- *ex vivo* models. Moreover, DCD was the highest at point F in the 8 cm- *ex vivo* model (Table II).

DMD was the highest at point A in the 2 cm-*ex vivo* model, whereas it was the highest at points B and C in the 8 cm- *ex vivo* model. Furthermore, DMD was the highest at points D, F, and G in the 4 cm- and 8 cm-*ex vivo* models, whereas it was the highest at points E and H in the 2 cm- and 4 cm-*ex vivo* models (Table III).

To determine the optimal nozzle position, we counted the number of highest DCD and DMD values in the three *ex vivo* models. The 4 cm-*ex vivo* model showed the highest score of 5 in the DCD and DMD values, suggesting that it could maximize aerosol delivery to about 62.5% of the area in this model (Figure 5).

Discussion

This study showed that the 4 cm- and 8 cm-*ex vivo* models showed greater number of stained faces than the 2 cm-*ex vivo* model in terms of the distribution of 1% methylene blue. With regard to the penetration depth of doxorubicin, the 4 cm-*ex vivo* model showed the highest DCD (mean; 244.1 μm, C; 105.1 μm, D; 80.9 μm, E; 250.2 μm, G; 250.2 μm, H) and DMD (mean; 174.8 μm, D; 162.7 μm, E; 511.7 μm, F; 522.2 μm, G; 528.1 μm, H) in the most points corresponding to 62.5%. These findings suggest that the ideal nozzle position during PIPAC may be halfway between the trocar site for inserting the nozzle and the surface of visceral organs located on the opposite side, contrary to previous studies where the position of the nozzle was ideal as it was closer to the surface of visceral organs located on the opposite side of the trocar site.

In general, the advantage of PIPAC is that agents are converted into aerosols during PIPAC, which can be evenly distributed in the abdominal cavity when sprayed by a high-pressure injector. However, there is not much basis for the quantitative evaluation of the distribution and penetration depth of the agents after PIPAC. Although some studies reported the homogeneous spatial distribution of methylene

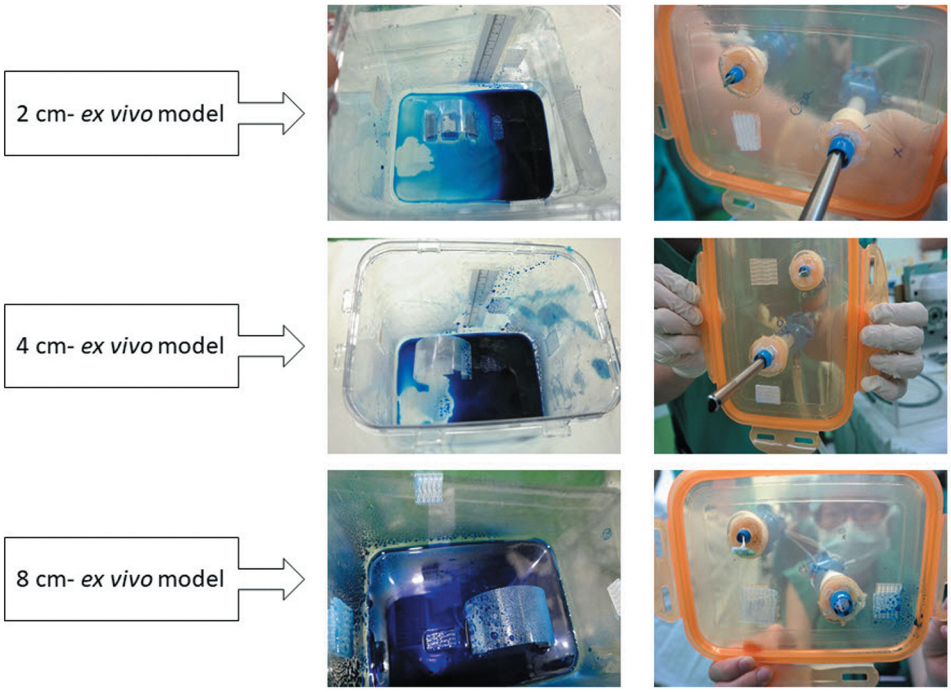


Figure 3. *The spatial distribution of aerosolized methylene blue during pressurized intraperitoneal aerosol chemotherapy in the three ex vivo models according to the distance between the nozzle and the bottom (2, 4, and 8 cm).*

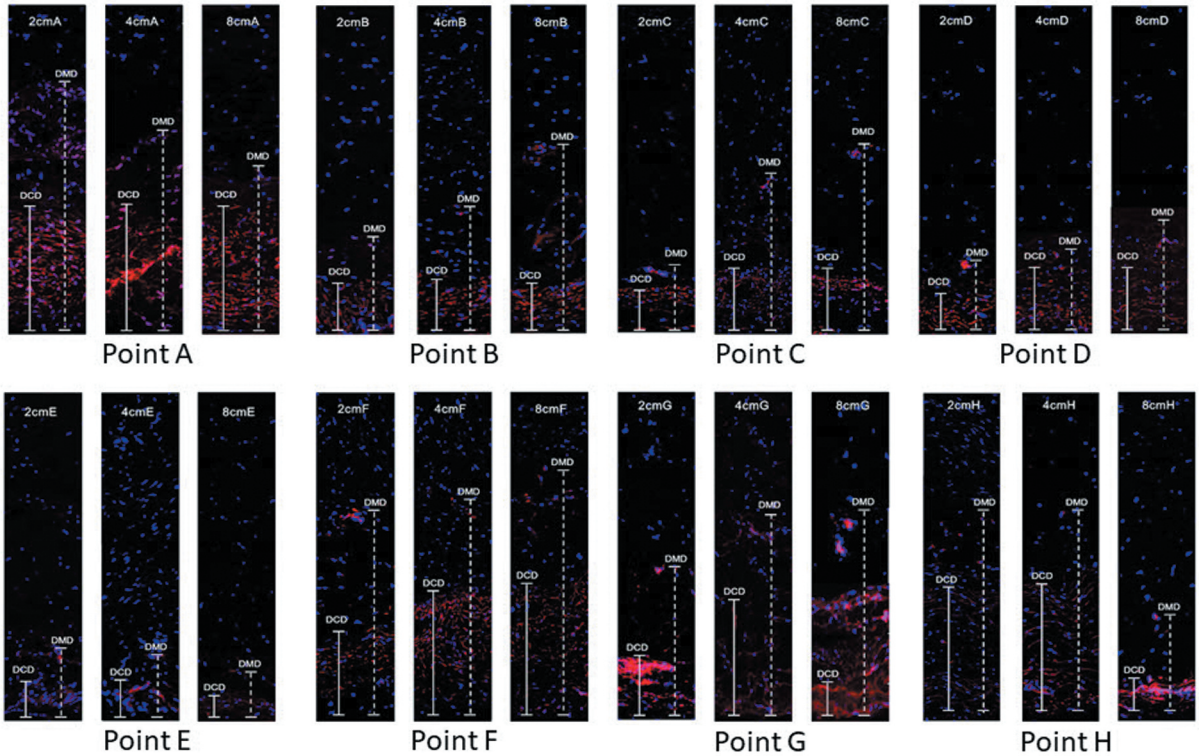


Figure 4. *Microscopic confocal laser analysis evaluating the depth of concentrated diffusion (DCD) and the depth of maximal diffusion (DMD) after pressurized intraperitoneal aerosol chemotherapy at points A to H in the three ex vivo models according to the distance between the nozzle and the bottom (2, 4, and 8 cm).*

Table II. *Comparison of DCD at points A to H among 2 cm-, 4 cm- and 8 cm-ex vivo models according to the distance between the nozzle and the bottom.*

Points	Three *ex vivo* models			*p*-Value
	2 cm-	4 cm-	8 cm-	
A	268.7±23.5*	265.1±18.5*	256.4±3.1*	0.88
B	133.9±4.5*	131.3±3.8*	133.2±3.5*	0.73
C	125.4±4.5	244.1±12.9*	245.3±12.1*	0.06
D	94.4±5.2*	105.1±3.9*,†	114.4±9.8†	0.04
E	84.7±1.8*	80.9±1.6*	57.6±1.1	0.03
F	174.8±5.3	244.1±9.3	265.5±6.1	0.03
G	111.2±5.9	250.2±9.5*	258.8±5.4*	0.05
H	257.9±6.8*	250.2±7.8*	92.8±3.4	0.05

DCD, Depth of concentrated diffusion; point A, on the bottom in the direct extension of the nozzle; point B, on the left side face, which is located in the middle of the entire height; point C, on the top face, which is located 3.5 cm away from the nozzle in the direction opposite from point D; point D, on the top face, which is placed opposite point F; point E, on the right side face, which is located in the middle of the entire height; point F, on the inner side of the barrier where both sides is open. Values labelled with the same characters (*, †) are not significantly different. All values are shown as mean±standard deviation (μm).

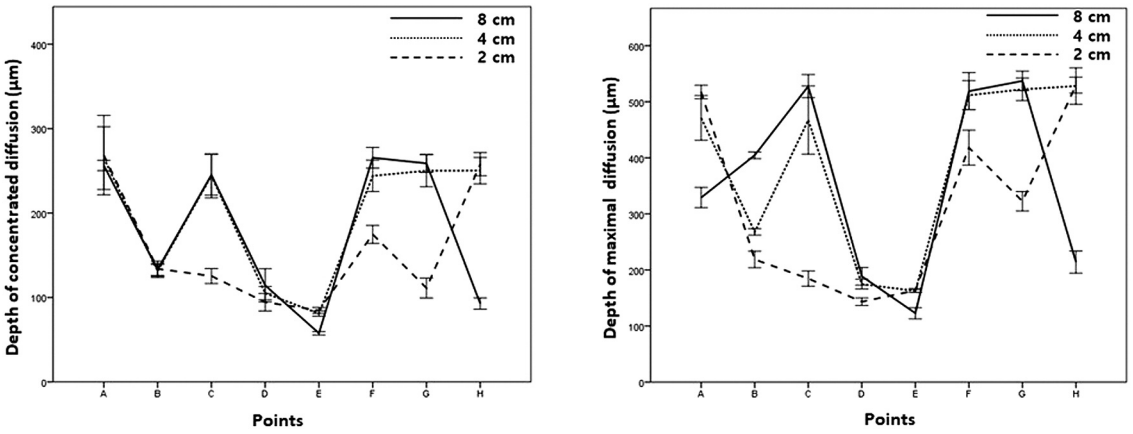
Table III. *Comparison of DMD at points A to H among 2 cm-, 4 cm- and 8 cm- ex vivo models according to the distance between the nozzle and the bottom.*

Points	Three *ex vivo* models			*p*-Value
	2 cm-	4 cm-	8 cm-	
A	517.5±6.1	471.2±19.9	329.1±8.9	0.03
B	218.7±7.4	267.9±2.8	404.6±2.9	0.03
C	184.6±6.8	467.4±30.4	527.7±10.3	0.03
D	143.4±3.4	174.8±4.4*	188.7±7.8*	0.03
E	163.4±1.7*	162.7±1.3*	122.8±5.1	0.06
F	418.2±15.6	511.7±13.1*	518.9±16.5*	0.06
G	322.5±8.7	522.2±10.1*	537.2±8.7*	0.04
H	529.8±7.1*	528.1±16.3*	214.1±9.9	0.06

DMD, Depth of maximal diffusion; point A, on the bottom in the direct extension of the nozzle; point B, on the left side face, which is located in the middle of the entire height; point C, on the top face, which is located 3.5 cm away from the nozzle in the direction opposite from point D; point D, on the top face, which is placed opposite point F; point E, on the right side face, which is located in the middle of the entire height; point F, on the inner side of the barrier where both sides is open. Values labelled with the same characters (*, †) are not significantly different. All values are shown as mean±standard deviation (μm).

blue after PIPAC in swine (23, 24), granulometric analyses demonstrated that CapnoPen® used in PIPAC made aerosols with a median diameter of 25 μm, and more than 97.5 vol% of the aerosol was delivered as droplets greater than 3 μm in diameter. Moreover, more than 86 vol% of the aerosol made by CapnoPen® was deposited within a 15-cm diameter circular area in several *in vitro* experiments, which suggests that it does not produce a homogeneous distribution of agents during PIPAC (16). Moreover, relevant *in vivo* and *ex vivo* studies showed that the penetration depth of the agents was the highest at a point opposite the Capnopen® (200-470 μm), whereas it was minimal at other points (20-150 μm) (18-20), suggesting that the current PIPAC system may lead to inhomogeneous distribution in the abdominal cavity. To overcome these limitations of the current PIPAC system, we developed the new nozzle, DreamPen®, with the comparable highest penetration depth of agents with CapnoPen® in more points by changing the injection pressure and outlet size (21).

For investigating the ideal nozzle position to maximize the distribution and penetration depth of agents in this study, we changed the points where tissue specimens were placed in the same plastic box used in previous studies to reproduce the structure of the abdominal cavity in the human body that may be asymmetric due to tumors or adhesions (18, 19). As



Ex vivo models	A	B	C	D	E	F	G	H	No. of the highest values (%)
Depth of concentrated diffusion (DCD)									
2 cm-					O			O	2/8 (25)
4 cm-			O	O	O		O	O	5 (62.5)
8 cm-			O	O		O	O		4 (50)
Depth of maximal diffusion (DMD)									
2 cm-	O				O			O	3 (37.5)
4 cm-				O	O	O	O	O	5 (62.5)
8 cm-		O	O	O		O	O		5 (62.5)

Figure 5. *The number of highest the depth of concentrated diffusion (DCD) and the depth of maximal diffusion (DMD) values in the three ex vivo models according to the distance between the nozzle and the bottom (2, 4, and 8 cm).*

a result, we obtained the following three meaningful results. First, DCD did not differ at the point opposite the nozzle in the three *ex vivo* models. A previous study defined penetration depth as the distance between the luminal surface and the innermost positive staining, which was similar to DMD in this study. It showed that the penetration depth of doxorubicin decreased with increasing distance between the nozzle and the bottom (18). Although this study also showed a similar DMD pattern in the three *ex vivo* models, we noted no difference in DCD where doxorubicin was mostly penetrated regardless of the distance between the nozzle and the bottom. Considering that the previous study showed that higher concentrations of doxorubicin led to an increase in the penetration depth, we could hypothesize that DMD might depend on the total doxorubicin dose delivered to the peritoneum, which might increase with a shorter distance between the nozzle to the bottom (18-21).

Secondly, DMD also did not decrease at all points other than the opposite point to the nozzle, unlike previous studies. Previous studies showed consistent results that greater doxorubicin penetration depth after PIPAC was observed only at points opposite the nozzle while lower values were observed at the other points (18, 20, 22), which contradicts the suggestion that PIPAC could lead to a homogeneous distribution of agents in treating PM (21, 24). In contrast, this study showed that higher DCD and DMD values were observed at different points depending on the distance between the nozzle and the bottom. Although asymmetrical positioning of the tissue specimens may have led to this diversity in values of DCD and DMD, the velocity of the aerosol made by the novel prototype can be considered the leading cause. In conventional PIPAC, aerosols are injected into the peritoneal cavity with a velocity of 60 km/h (25), whereas the velocity of the aerosol was about 5 km/h in the novel prototype (21). Since the flow rates were similar at 30 ml/min and the aerosol diameter between conventional PIPAC and the novel prototype was similar, we can infer that the injection outlet size through which the aerosol passes from the nozzle may be larger in the novel prototype. A lower aerosol velocity and larger injection outlet size could reduce the turbulent flow of the aerosol in the novel prototype (26). Moreover, most of the injected aerosol may move according to the inertia created by the injection pressure, and collisions allowed the aero-sol to move to various locations in the

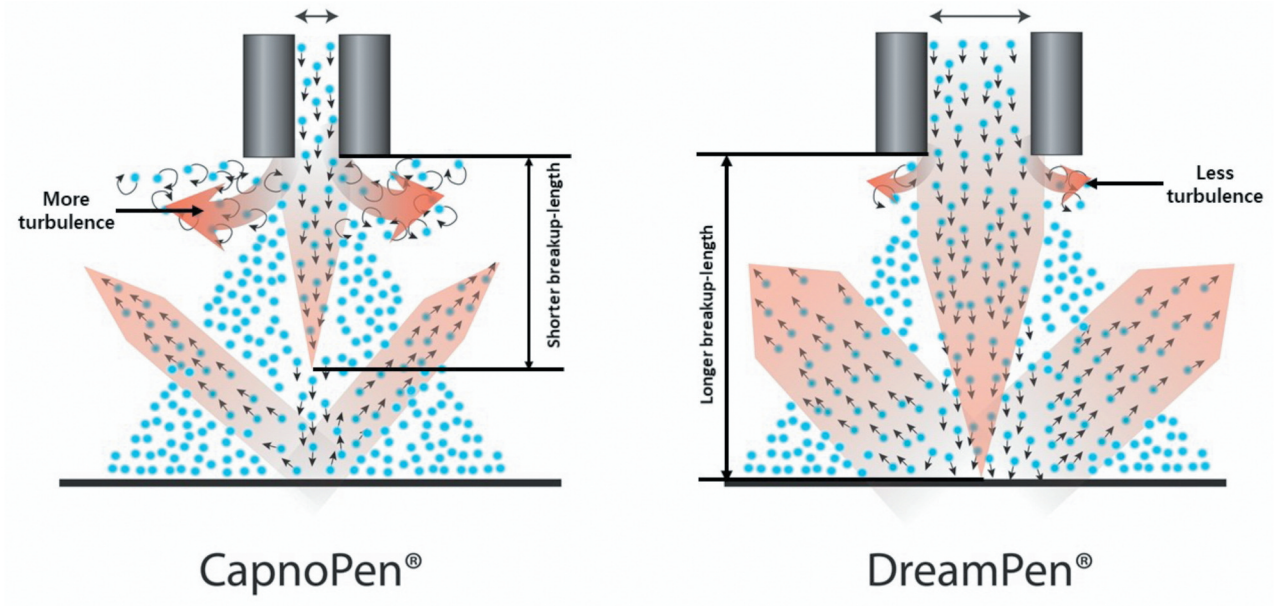


Figure 6. *Hypothesis about the movement of the aerosol-based on the injection velocity and outlet size. CapnoPen® can show more turbulence and less deflection by the collision of the aerosol because of shorter breakup-length within the sprayed zone, whereas DearmPen® can show less turbulence and more deflection by the collision of the aerosol because of longer breakup-length within the sprayed zone.*

peritoneum may be more increased in DreamPen® than in CapnoPen® by longer breakup-length within the sprayed zone, which may lead to increased movement of the aerosol by an increase of deflection (Figure 6) (27, 28).

Considering this complex motion of aerosol sprayed during PIPAC, we found that the 4 cm-*ex vivo* model was the most appropriate for PIPAC in this study. Previous studies suggested that the diameter of aerosols should be less than 1 μm for homogeneous diffusion in a gas-like form during PIPAC (29, 30). However, in practice, both large droplet sizes may directly impact the peritoneum or precipitation due to gravity (19). Since large aerosol sizes precipitate due to gravitational forces and inertia according to fluid mechanics (27, 30), the results from this study suggest that the ideal nozzle position should be determined by the three-dimensional structure of the human abdominal cavity, considering that intraperitoneal tumors or adhesions can affect the movement and deflection of the aerosol droplets. In particular, this study also suggests that the closer the nozzle is from the bottom, the more the aerosol may be unevenly distributed.

Nevertheless, this study had certain limitations. First, we evaluated the ideal nozzle position in normal *ex vivo* models not reflecting PM. Thus, location and adhesion of tumors, movement of the peritoneum by respiration and bowel peristalsis, and stretch of the peritoneum under capnoperitoneum can affect patterns of the distribution and penetration depth of agents. Second, the ideal nozzle position based on the distance between the nozzle and the bottom can be considered one of the various parameters, including the injection angle in this *ex vivo* model. Thirdly, experiments in a 36˚C water bath environment without vascularity and lymphatics have limitations from those in the human body even though the spatial distribution pattern was investigated by *ex vivo* experiments using fresh postmortem swine peritoneum. Thus, we planned a study to evaluate the optimal position of DreamPen® during PIPAC for its efficacy and safety by using a large animal model with PM. Fourth, delayed uptake and lymphatic transport can make up for unequal distribution and accumulation of aerosol despite the importance of diffusion and tissue penetration suggested in PIPAC. Fifth, the role of the optimal position of the nozzle for treating PM should be clinically investigated because the current set-up of the nozzle has shown encouraging clinical results in various types of solid tumors with PM (13). Sixth, the movement of aerosol due to gravity, inertia, and deflection should be studied in more detail based on fluid mechanics.

On the other hand, this study also has certain strengths as follows: First, DreamPen® can have the potential to provide complex movement of aerosol, contrary to CapnoPen® showing the limited distribution and penetration focused on the opposite side of the nozzle. Second, this complex movement of aerosol can lead to the improvement of drug delivery into the peritoneum for patients with PM.

In conclusion, this study suggests that a 4 cm-*ex vivo* model may be the most appropriate for PIPAC using

DreamPen® contrary to that of CapnoPen® optimized in 2 cm-*ex vivo* model due the complex movement of aerosol made by DreamPen®. However, the optimal position of DreamPen® for PIPAC can differ among patients with PM, which should be determined by the three-dimensional structure of the human abdominal cavity with intraperitoneal tumors or adhesions in clinical setting. For overcoming the limitation that it is clinically difficult to determine the optimal nozzle position in patients with PM, the nozzle that can be rotated or adjusted can be expected to improve diffusion and penetration of aerosol during PIPAC (31). Furthermore, PIPAC with the ideal nozzle position for enhancing drug delivery could be introduced to treat advanced or recurrent gynecologic cancers with PM, particularly ovarian cancer (32).

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Jinlan Piao: Methodology, formal analysis, investigation, writing the original draft, visualization. Soo Jin Park: Methodology, formal analysis, investigation, writing the original draft, visualization. Heesu Lee: Conceptualization, methodology, software, resources, data curation. Junsik Kim: Conceptualization, methodology, software, resources, data curation. Sunwoo Park: Conceptualization, methodology, validation, investigation. Nara Lee: Conceptualization, methodology, writing the revised draft. Se Ik Kim: Conceptualization, methodology, writing the revised draft. Maria Lee: Conceptualization, methodology, writing the revised draft. Gwonhwa Song: Conceptualization, methodology, validation, investigation, supervision. Jung Chan Lee: Conceptualization, methodology, validation, investigation, supervision. Hee Seung Kim: Conceptualization, methodology, formal analysis, resources, writing original draft, supervision, project administration, funding acquisition.

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