Master's Thesis of Engineering

Development of a Novel Pressurized Intraperitoneal Aerosol Chemotherapy System with a Conical Pendulum Motion Device

원뿔 진자 운동을 이용한 고압항암화학 요법 기기 개발

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Abstract

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Colorectal and ovarian cancers are two types of pelvic tumors known for poor prognosis due to recurrence. These two cancers are often associated with the incidence of peritoneal carcinomatosis (PC) during recurrence. Due to its poor survival rate and limited treatment options, PC is considered as a terminal stage of cancer for patients. Local drug administration in intraperitoneal chemotherapy such as early postoperative intraperitoneal chemotherapy (EPIC) and heated intraperitoneal chemotherapy (HIPEC) has been adopted as a therapeutic indication for many years. However, there are some limitations of EPIC and HIPEC. Those are not significantly effective for patients, and there are some crucial complications.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been introduced as an alternative approach for PC treatment which delivers chemotherapeutic drugs into the abdominal cavity in aerosol while maintaining the abdominal pressure at 12 mmHg with carbon dioxide. Drug particles are sprayed and floating the room of peritoneal cavity, and the pressure makes drugs penetrate tissues. PIPAC treatment does not have complications rather than conventional treatments and could be performed repetitively. Even though PIPAC uses 10% and 20% of a significantly lower dose chemotherapeutic drugs compared to the intravenous chemotherapy dosage and HIPEC respectively, it delivers drugs directly to the tumor tissues increasing the local chemotherapy concentration since drugs only affect at specific region. However, current PIPAC treatment also has a disadvantage that it does not guarantee homogeneous drug distribution. To overcome these limitations of current options, a novel PIPAC system with a conical pendulum motion device has been developed. The nozzle has been made the nozzle to alternate current PIPAC's nozzle(Micropump) to optimize the particle size, wider distribution and deeper penetration depth. Also, a conical pendulum motion device has been applied to widen drugs distribution which is sprayed directly. With the prototype, experiments have been performed to test nozzle performance and PIPAC performance in this study. It has been demonstrated that our nozzle performance is slightly improved than Micropump performance in terms of drugs distribution and penetration depth. Moreover, through In-vivo experiment, it has been proved that using a conical pendulum motion device makes superior results which affect larger regions in peritoneal cavity rather than using a nozzle alone.

Keyword : Peritoneal carcinomatosis (PC), Heated intraperitoneal chemotherapy (HIPEC), Pressurized intraperitoneal aerosol chemotherapy (PIPAC), Conical pendulum motion

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List of Abbreviations

PC	Peritoneal Carcinomatosis
EPIC	Early Postoperative Intraperitoneal Chemotherapy
HIPEC	Heated Intraperitoneal Chemotherapy
PIPAC	Pressurized Intraperitoneal Aerosol Chemotherapy

Chapter 1. Introduction

1.1 Peritoneal Carcinomatosis(PC)

Colorectal and ovarian cancers are two types of pelvic tumors known for poor prognosis due to recurrence. Over 1.8 million new colorectal cancer cases and 881,000 deaths are estimated to occur in 2018. Colorectal cancer has the third highest incidence and the second mortality rate worldwide in 2018[1]. It has higher incidence and mortality for both sex. Ovarian cancer is also known for its low survival and high incidence rates. It has the eighth highest incidence and mortality rate in females worldwide[1]. Also, the incidence of incidence is increasing recently.

These two malignancies are mainly associated with the higher incidence of peritoneal carcinomatosis (PC) during recurrence. PC is intraperitoneal dissemination of any form of tumor that is not originated from the peritoneum itself. PC is one of the most common diffuse peritoneal diseases. More than 50% of colorectal and ovarian patients develop PC and life expectancies of less than 20 months and 10 months, respectively even with surgery and chemotherapeutic treatment options[2]. Due to its poor survival rate and limited treatment options, PC is considered as a terminal stage of cancer for patients. Therefore, the novel treatment of PC must be developed soon.

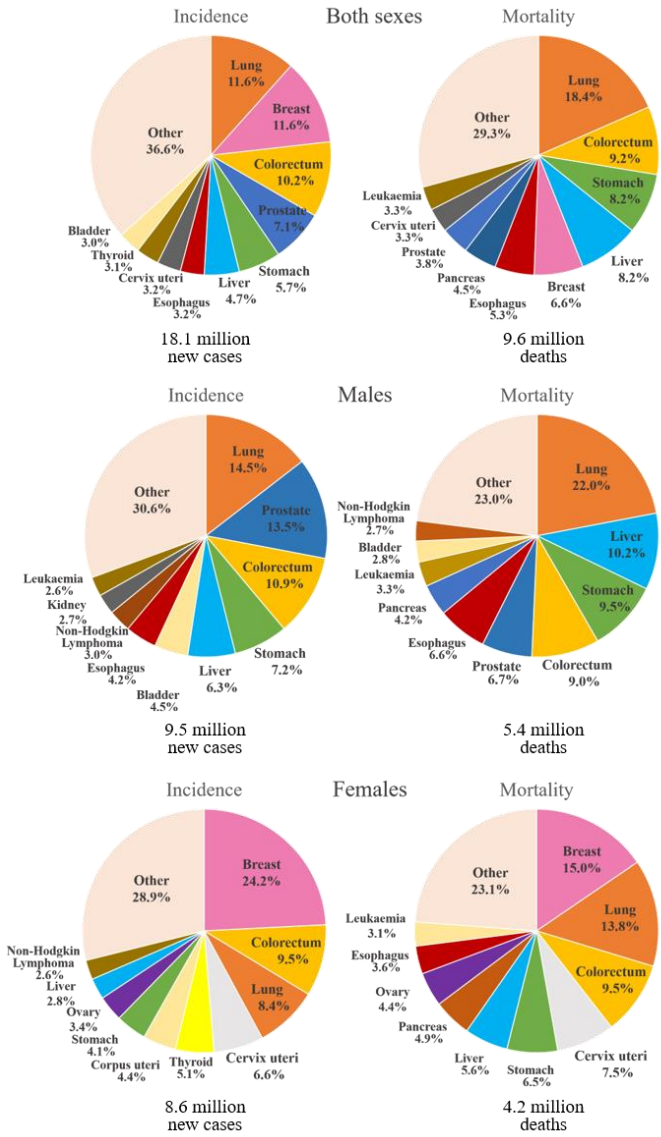

Figure 1-1. Pie charts for global cancer

Each figure shows the distribution of cases and deaths for the 10 most common cancers in 2018 for (A) Both Sexes, (B) Males, and (C) Females[1].

1.2 Treatment Options and Limitations

Local drug administration in intraperitoneal chemotherapy has been adopted as a therapeutic indication for many years. Early postoperative intraperitoneal chemotherapy (EPIC) and Hyperthermic intraperitoneal chemotherapy (HIPEC) have been offered as effective treatment methods for PC[3]. EPIC targets the tumor cells in the peritoneal cavity by directly administering chemotherapeutic drugs into the abdomen. Abdomen minimizing side effects of intravenous chemotherapy. HIPEC, a treatment with a high concentration of heated chemotherapy drug solution, has been developed to eliminate remaining cancer cells after chemotherapeutic surgery[4]. During HIPEC procedure (Figure 1-2), 41~43℃ of high temperature chemotherapy drug solution is perfused in peritoneal cavity to remove cancer cell's microtubule system. For multiple studies, HIPEC has been shown to be affected to extended survival compared to systemic chemotherapy alone[5].

However, both EPIC and HIPEC still have considerable limitations. The treatment options demonstrate unsatisfactory distribution of drugs across the peritoneal cavity and offer penetration depth of drugs into the tumor tissue less than 1 mm, leaving tumor tissues untreated[3, 6]. Also, patients undergoing HIPEC may develop complications due to the injection of high-temperature drugs. HIPEC related complications are relatively frequent and typically renal toxicity, cardiac toxicity and hepatic toxicity. Previous study reported these complications were significant causes which affected to the morbidity [7].

For these reasons, there is a need to overcome a variety of weaknesses in current chemotherapy for peritoneal carcinomatosis patients.

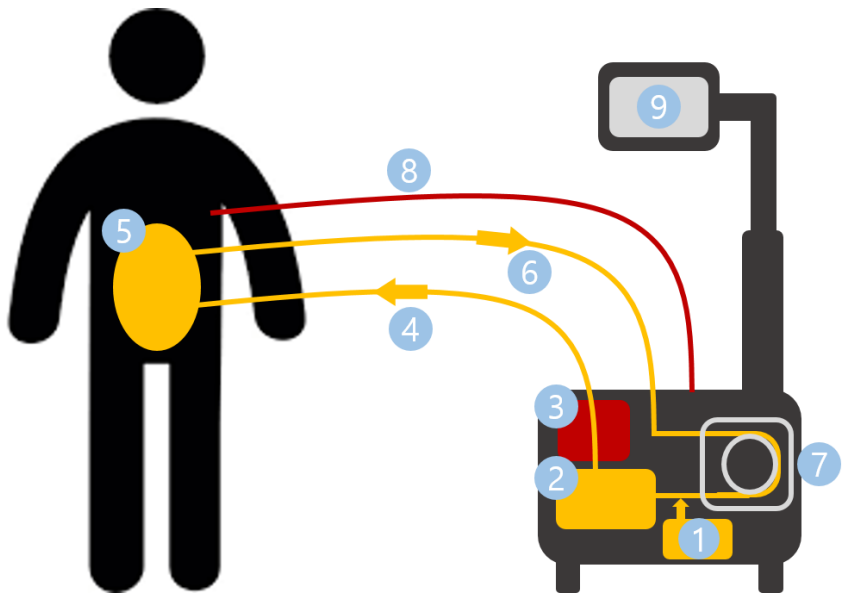

Figure 1-2. Schematic overview of HIPEC

Drugs (1) inject to the line and mixed in reservoir (2). This solution is heated by a heater (3) maintaining 41~43℃ and delivered to patients' peritoneal cavity through inflow catheter. The thermometer (8) checks the inner temperature of peritoneal cavity. And then chemotherapeutic drugs circulate to reservoir through outflow catheter (6) via pump (7). All condition of operation is displayed in monitor (9)[8].

1.3 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been introduced in Europe as an alternative approach for peritoneal carcinomatocis treatment overcoming the limitations of EPIC and HIPEC[9].

Figure 1-4 shows the principle of PIPAC. PIPAC delivers aerosolized chemotherapeutic drugs into the abdominal cavity via nebulizer (MIP; Capnomed GmbH, Villigendorf, Germany) and high-pressure injector (Arterion 7; Medrad, Bayer Healthcare, Medrad Europe, Maastricht-Airport, Netherlands) while maintaining the abdominal pressure at 12 mmHg with carbon dioxide[10]. The nebulizer and high-pressure injector which are used in PIPAC are shown in Figure 1-3. Whole process is operated with a laparoscopy and nebulizer, instead of surgical equipment, is inserted into trocar.

After spraying chemotherapeutic drugs, the aerosolized drugs floating in the cavity penetrates tumor tissues due to gas influx at the pressure of 12 mmHg for 30 minutes, and the drug penetration depth increases accordingly. At the end of the PIPAC procedure, aerosolized drugs are discharged through filter to vacuum system[11].During PIPAC treatment, all clinicians have to exit the operation room due to the hazard of the chemotherapeutic drugs. Therefore, PIPAC equipment has to be controlled remotely.

PIPAC has also demonstrated improvement in drug efficacy and safety by reducing the systemic effect of chemotherapy. Even though PIPAC uses 10% and 20% of a significantly lower dose chemotherapeutic drugs compared to the intravenous chemotherapy dosage and HIPEC respectively, it delivers drugs directly to the tumor tissues increasing the local chemotherapy concentration since drugs

only affect at specific region[12, 13]. The direct delivery method has also allowed for the treatment of patients with recurrent, platinum-resistant ovarian cancer[12]. Also, minimal renal and hepatic toxicities have shown in PIPAC treated patients unlike those with HIPEC treatment[10]. Also PIPAC treatment has advantage that it can be conducted repetitively.

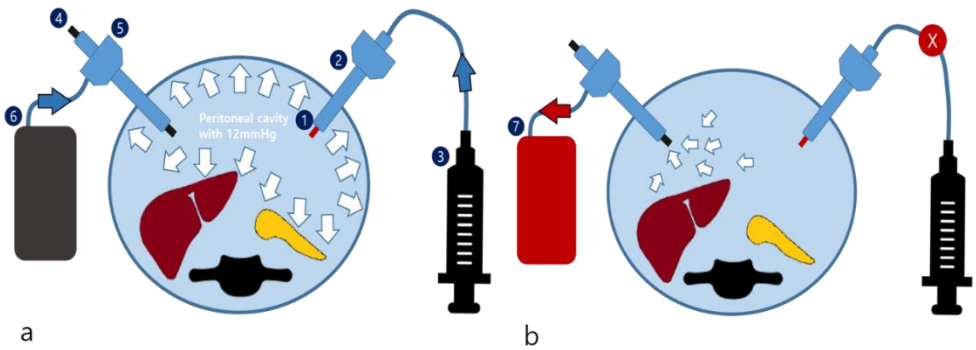

Figure 1-3. Principle of pressurized intraperitoneal aerosol chemotherapy(PIPAC)

(A) During a laparoscopy with CO2 insufflation (6) a pressure of 12 mmHg, at a temperature of 37 ℃. A nebulizer (1) is inserted into an access trocar (2) and drugs are pushed by high pressure injector (3). It is operated via video control (4) with a 5mm trocar (5).

(B) At the end of the procedure, the injector is stopped and remaining aerosolized drugs are released over a closed aerosol waste system into the external environment (7)[14].

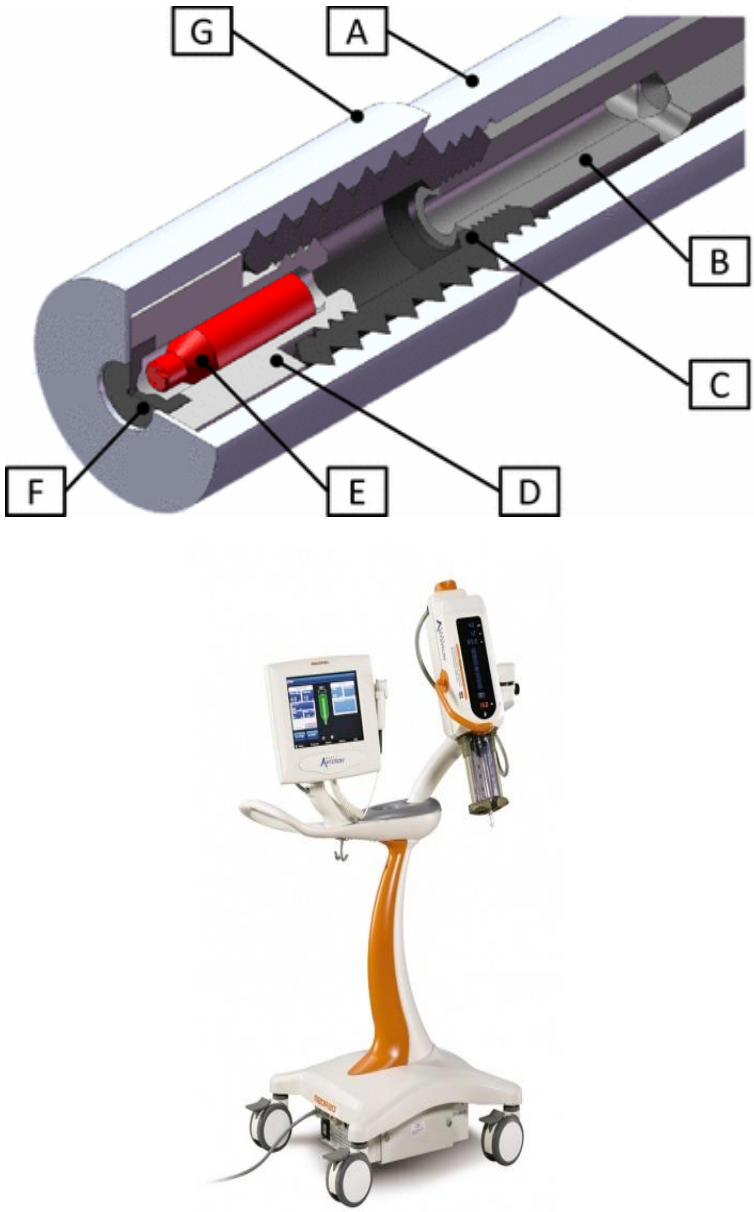

Figure 1-4. Geometry of the MIP and High-pressure injector which are used in the current PIPAC [15]

1.4 Limitation of PIPAC

Several challenges lie ahead of the PIPAC system. Currently, PIPAC devices including MIP do not guarantee homogeneous drug distribution across the peritoneal cavity. Previous ex-vivo studies have investigated the efficacy of MIP using tissue samples with different locations, different drug concentrations and different pressure in a plastic box simulating the peritoneal cavity[16].

The drug penetration depth was significantly notable only in the tissues installed directly opposite to the Micropump nebulizer. The tissue samples located on the side walls, above the tip of the nozzle and covered by plastic showed significantly lower penetration depth[3, 16]. Due to this non homogeneous distribution pattern, efforts have been made to develop devices that can overcome the current limitations of PIPAC[17-19]. However, the prototypes introduced in these studies have not been extensively investigated for their performances and have not demonstrated improved penetration depth or drug distribution. Therefore, limitations regarding the penetration depth and drug distribution still remain[20].

To overcome these weaknesses, most of researchers have focused on improving the aerosolization of chemotherapeutic drugs[3]. They have demonstrated that aerosol droplets are supposed to behave nearly ‘gas- like’ so that gas-like drug can float in peritoneal cavity everywhere. Such a system, however, requires even higher pressure than that of the current system. Moreover, the evaporation of liquid drug takes long time and gas chemotherapeutic drugs is extremely hazard for clinicians.

However, they have not tried to spray chemotherapeutic drugs with wide range of distribution. Therefore, this research focuses on developing the device which can spray much wider distribution.

1.5 Research aims

There exists a need for improvement of PIPAC regarding the tissue penetration depth and distribution area of chemotherapeutic drugs to expand treatment options for PC patients.

Therefore, the aim of research is developing a novel PIPAC system with a conical pendulum motion device. Firstly, a novel nozzle which does the same role as Micropump which is mentioned in previous studied has been developed. Secondly, to spray drugs with high pressure, syringe pump which is made of aluminum and geared stepper motor has been developed. Finally, to extend distribution range of chemotherapeutic drugs wider, conical pendulum motion device has been made.

With these three components, two kinds of tests have been performed. First, it was performed that the nozzle performance to prove the valuable property as PIPAC nebulizer itself. Second, the PIPAC performance has been accomplished with In-vivo experiment to verify its efficacy as PIPAC treatment using nozzle alone and using conical pendulum device.

Chapter 2. Methods

2.1 Components of Prototype

2.1.1 Description of the Nozzle and Syringe Pump

- ***Geometry of the nozzle***

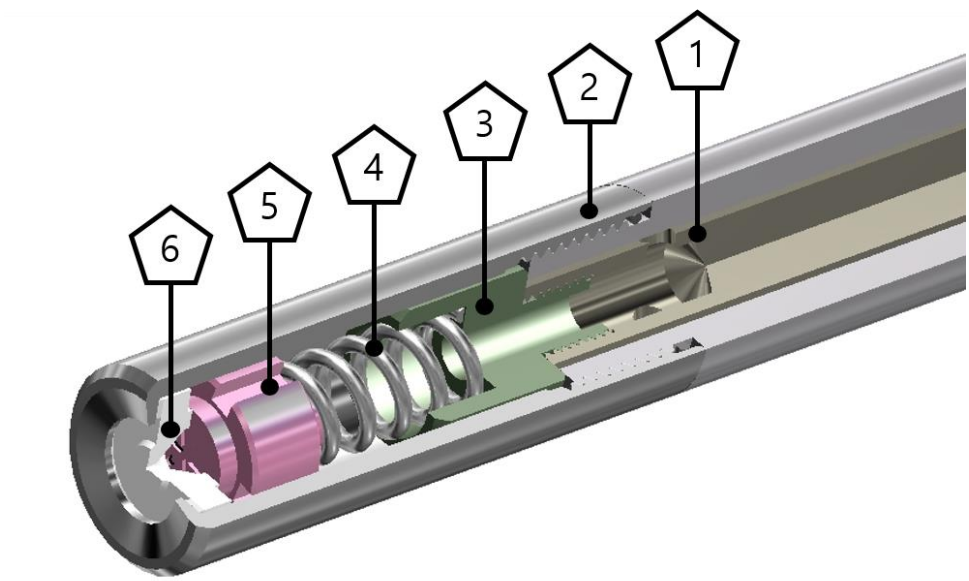

Figure 2-1. Model of the nozzle in 90° sectional view

The nozzle which is used in this paper is one of a single fluid nozzle. Figure 2-1 shows the 3-D 90° sectional drawing of the nozzle. Our nozzle is composed of 6 parts. Injection lance (1) is overall case that holds each component and it is first part that contact the liquid. The liquid enters the nozzle through the two holes in the sleeve (2) which was designed to reduce the liquid volume remaining in the body after injection. The liquid then travels through the empty compartment (3) that meets with a pushing spring (4). Finer particles are formed when the liquid is pushed through the spring, and the liquid particles flow through the groove (5). The particles enter the chamber between (5) and the nozzle tip (6), and the turbulence is formed. Because of the hexagonal groove at the bottom of part (5), the flow of air core is deformed so that spraying pattern is changed with full cone pattern. The particles get broken down finer and sprayed with a wide angle as a result of the centrifugal force and a high rotational speed of particles caused by the turbulence in the chamber as they leave the orifice and contact the air.

The diameter of the orifice is 0.2 mm and the diameter of the spray nozzle is 10 mm, which was designed to fit through a 12 mm trocar. The length of the spray nozzle was designed 30 cm to be longer than 12 mm trocar.

- ***Syringe pump***

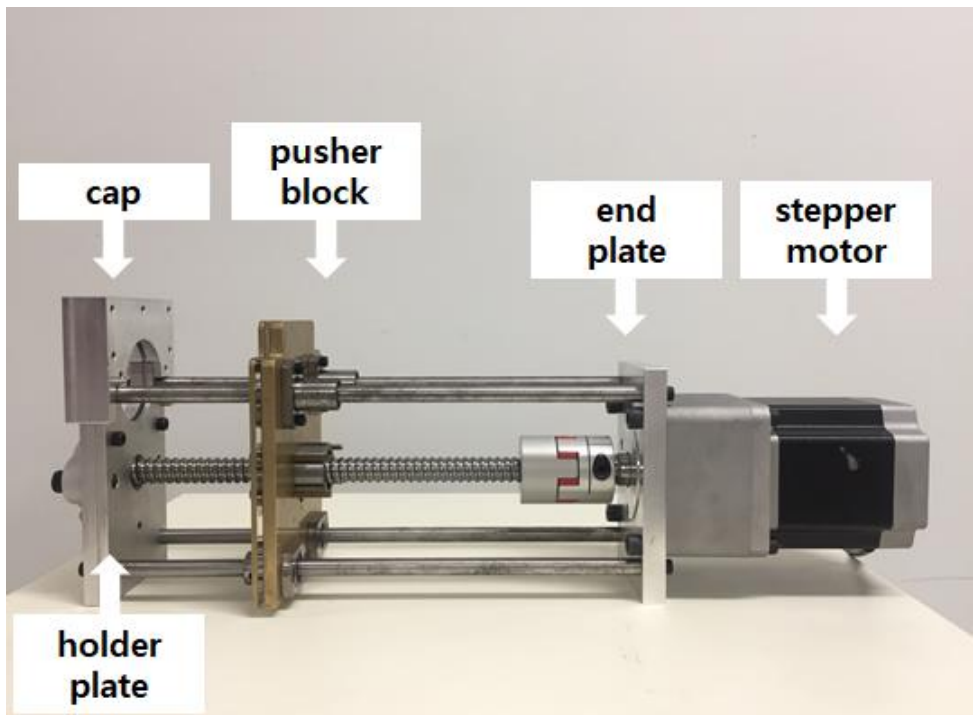

Figure 2-2. Components of high pressure syringe pump

The syringe pump developed in this is shown in Figure 2-2. Unlike the other syringe pump the whole part of our syringe pump is composed of aluminum and brass which can endure the high linear force that the geared stepper motor makes. It consists of 5 components, a stepper motor, a holder plate, a pusher block, an end plate, and a cap

As shown in Figure 2-2, the syringe pump consists of a geared stepper motor (A200K-G599W-G10, Autonics, Korea), an end plate, a pusher block, a syringe holder plate, a cap and a ball screw. The stepper motor used for the pump generates a maximum torque of 19.6 Nm and a maximum linear force of 1200N, which allows for 7 bars of pressure required for drug delivery. A ball screw was selected as a linear actuator connected to the stepper motor for its higher accuracy than a lead screw.

They were then secured to three blocks of the syringe pump. The three blocks consist of an end plate which is supporting the stepper motor and four rods, a pusher block which pushes the plunger of a syringe so that it makes the high pressure, and a holder plate that hold the finger grip part of a syringe. All blocks were CNC milled with aluminum and brass to endure high pressure applied to the blocks. Four rods were inserted to connect the blocks to serve as a guide rail.

Figure 2-3 shows the assembly of the nozzle and syringe pump with a syringe. This study adopted 200ml syringe since 150ml of chemotherapeutic drugs solution volume has been used in typical PIPAC treatment[2]. Therefore, our syringe pump is interlocked with only 200ml syringe. In detail, holder plate is designed to be fit only 200ml syringe.

The syringe can be inserted and snapped into the retainer brackets incorporated in the pusher and holding blocks. The pusher block travels along the four rods and pushes the syringe end to deliver drugs with a high pressure when the actuator is driven while the holding block with an aluminum cap over the syringe prevents the bending and breakage of syringe due to the pressure.

Drugs are delivered syringe to nozzle via Polytetrafluoroethylene(Teflon) tube. Teflon tube is selected due to its acid resistant material and its hardness which can endure 7 bar of high pressure. 200ml syringe is connected with female luer lock connector and it is arranged with PTFE tube by 2-touch-lock fitting. Also, the nozzle is linked with Teflon tube by 2-touch-lock fitting.

To reduce the remaining drugs, small inner diameter Teflon tube (4mm OD x 2mm ID) was used. The length of the tube is decided 140 cm regarding to optimize the length between operating table and syringe pump with a conical pendulum motion device.

An end-stop switch was attached to the holder plate to make the syringe pump stop automatically. After finishing the injection procedure, the syringe pump should not move forward. When a pusher block touches the end-stop switch which is fixed on the holder plated, the stop signal is go through the main board and it orders the syringe pump to stop moving automatically.

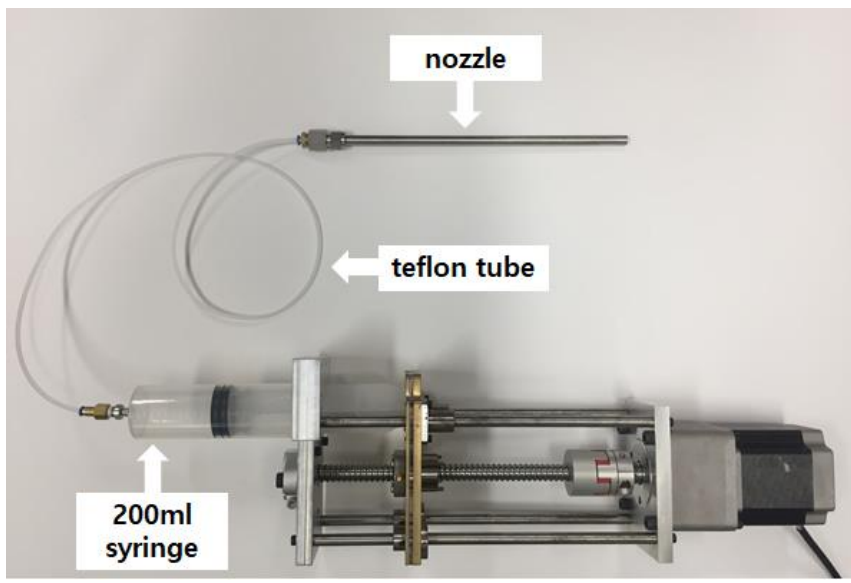

Figure 2-3. Components of PIPAC system

The PIPAC system consists of a syringe pump, a 200ml male luer lock syringe, and a spray nozzle connected to the syringe by a 4mm OD x 2 mm ID Teflon tubing. All tubing connections were made with appropriate luer lock fittings.

- ***Controller***

The stepper motor is driven by the main and remote controllers presented in Figure 2-4. The main controller consists of a twin output SMPS (DC 5V/3A, 24V/10A, SS-241052, EUN SUNG, Korea), two Arduino UNOs, HC-06 Bluetooth modules, and a touch screen (NX8048T070_011R, Nextion, USA). One controls the syringe pump and the other receives force values from the load cell. With twin output SMPS, a geared stepper motor is operated by 24V/10A and a touch screen is turned on by 5V/3A. The remote controller is made of an Arduino UNO, touch screen, HC-06 Bluetooth module and battery(9V).

Shown in Figure 2-5, the signal from the remote controller is transmitted to the main controller via the Bluetooth module. It then delivers to the stepper motor through a motor driver (MD5-HD14, Autonics, Korea) and motor is rotated by CW/CCW way.

A load cell (TAS606, HT Sensor Technology, China) attached to the pusher block measures the force when the syringe moves forward to deliver fluids to the nozzle. Pressure applied to the nozzle is calculated from the measured value of force and the area of the syringe. The calculated pressure value is transmitted to the Remote controller via HC-06 Bluetooth module and shown on the touch screen.

The touch screen presents the volume and flow rate of drug, pressure value, and remaining time until stop.

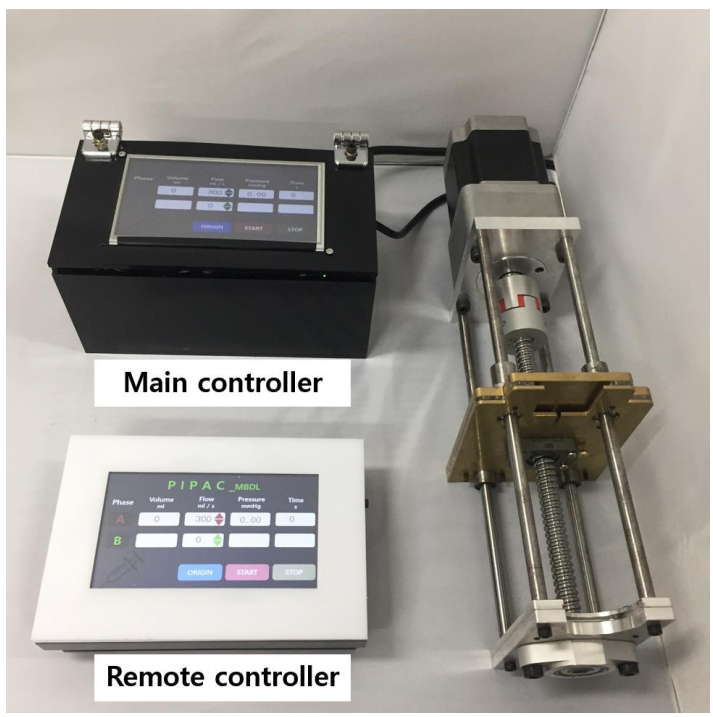

Figure 2-4. Main controller and Remote controller

These two controllers operate the syringe pump. Main controller is connected to the motor driver that transmits the signal and the motor driver is connected to the stepper motor directly. When remote controller transmits the signal to operate syringe pump via Bluetooth, main controller receives the signal via Bluetooth and transmits it to the motor driver.

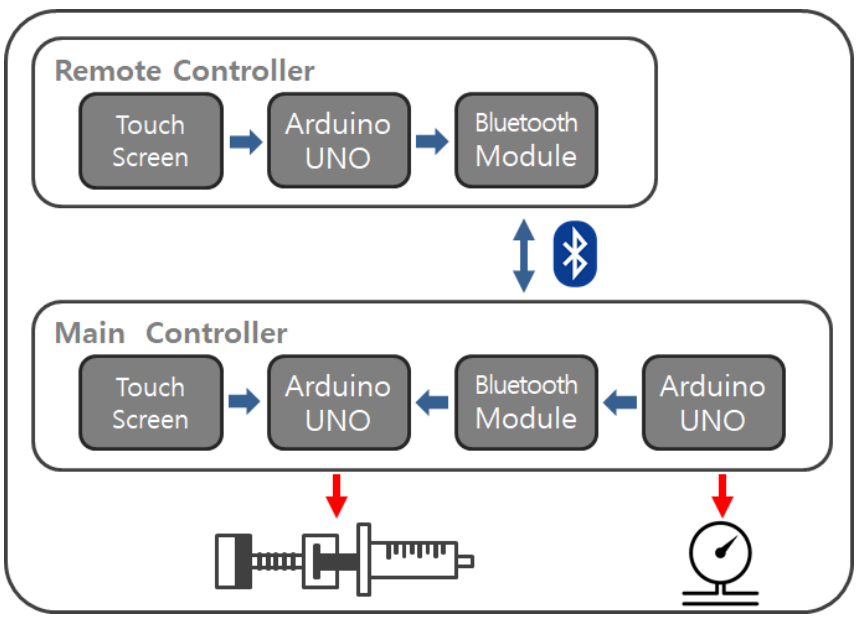

Figure 2-5. Schematic diagram of the controllers

Remote controller and main controller communicate via Bluetooth. Each controller has a touch screen that can control the speed of the syringe pump and on/off button. When remote controller transmits the signal, main controller receives the signal via Bluetooth and deliver the signal to the syringe pump through motor driver. Also main controller receives force values from the load cell and it is calculated to the pressure value that affects to the inner system.

2.1.2 Description of the Conical Pendulum Motion Device

Conical pendulum motion is similar to an ordinary pendulum motion. A simple pendulum consists of a relatively massive object suspended by a string from a fixed support(pivot). It typically suspended vertically in its equilibrium position. However, in conical pendulum, a massive bob revolves in a horizontal circle with constant speed at the end of a string tracing like a cone shape in Figure 2-6. It has been applied the upside – down conical pendulum motion to our device for improvement of the wider spraying distribution. Instead of massive bob, the nozzle revolves like a string which is tracing like a cone shape. Conical pendulum motion device consists of a DC motor (12V/1.5A, GM35A-3323, Motorbank, Korea), a 3-D printed rotational stick, two end-stops (PCB mounted End-stop switch, RepRap, England) and an Arduino Uno.

A high torque DC motor was selected since a motor is supposed to rotate with nozzle which is filled with chemotherapeutic drugs. Nozzle is inserted in a 3-D printed rotational stick and locked with screw. The angle between nozzle and vertical line is determined 30 degrees by calculating the spraying angle of approximately 70 degrees. The rotational stick moves repeatedly clockwise and counterclockwise. The stick cannot rotate same direction continually, because Teflon tube could be got tangled. It is controlled by an end-stop which is a switch that recognizes mechanical press and transmits the electronic signal to the main board.

In Figure 2-7, two end-stops are fixed on the motor box. There is a tip on the opposite side of the rotational stick which makes the nozzle rotate. When the tip touches the first end-stop, the signal goes to the main board and orders the stick to rotate counterclockwise. When the tip touches the other end-stop, the Arduino Uno commands the stick rotate clockwise. It keeps repeating this procedure during spraying chemotherapeutic drugs.

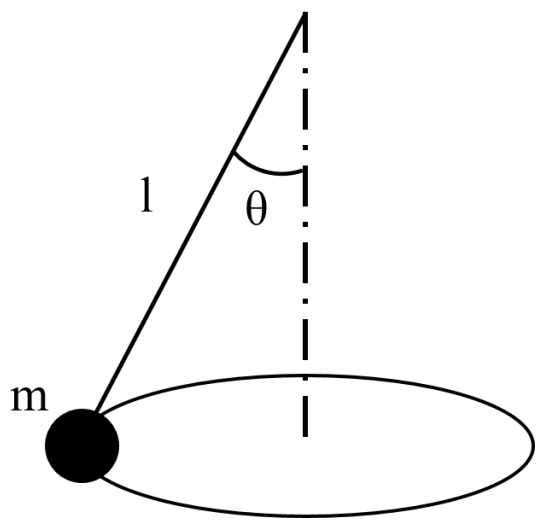

Figure 2-6. Conical pendulum motion

A conical pendulum consists of a bob and a string. m is the mass of a bob, l is the distance of a string and θ is the angle between a string and a vertical line.

It is similar to an ordinary pendulum motion, however, instead of swinging back and forth, the bob moves in a circle with the string making a virtual cone shape. This motion has been applied to widen the distribution range. Instead of a string, a nozzle whose spraying direction is the opposite of m was placed.

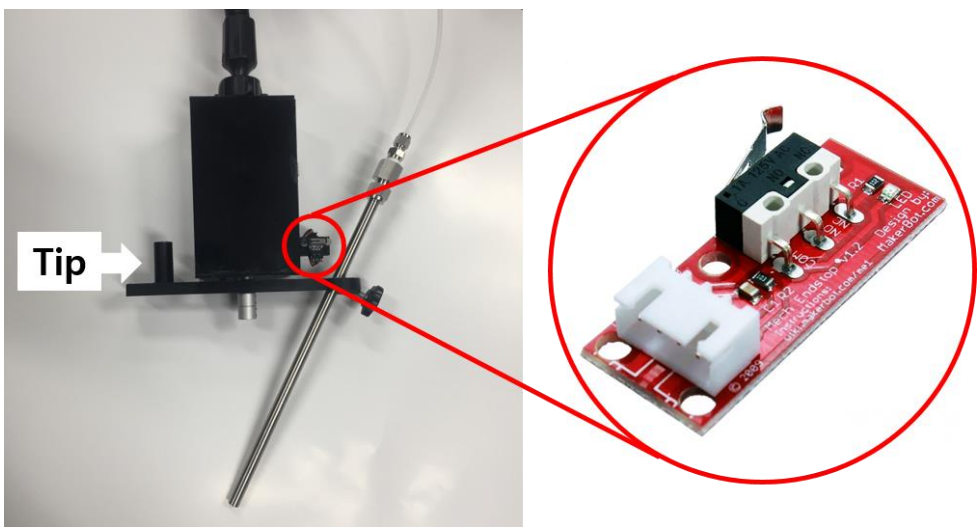

Figure 2-7. Conical pendulum motion device with end-stop switch

Left side of Figure 2-7 is conical pendulum motion device. Mechanical change which is made by a tip is utilized to rotate clockwise and counter clockwise. End-stop switch is on the right side of Figure 2-7. It acts for transmitting the signal from mechanical pushing change.

2.2 Nozzle Performance Test

2.2.1 Granulometric Analysis and Spray Angle analysis

As shown in Figure 2-8, Particle Dynamics Analysis (FiberPDA receiver, Dantec Dynamics, Denmark) was performed at Korea Institute of Machinery and Materials to measure particle velocity and its mean diameter. 20℃ deionized water was filled in a syringe and sprayed via the nozzle. Particle size and velocity were measured 12cm away from the orifice.

Also the angle of spraying nozzle was measured by a laser. It was projected 12cm apart from the orifice. The path of the laser was only shown where the particles were present. And then A picture of the side view of the spraying particles and the laser path was taken. The angle was derived from the distance between the orifice and the visible length of the laser path using the Pythagorean theorem.

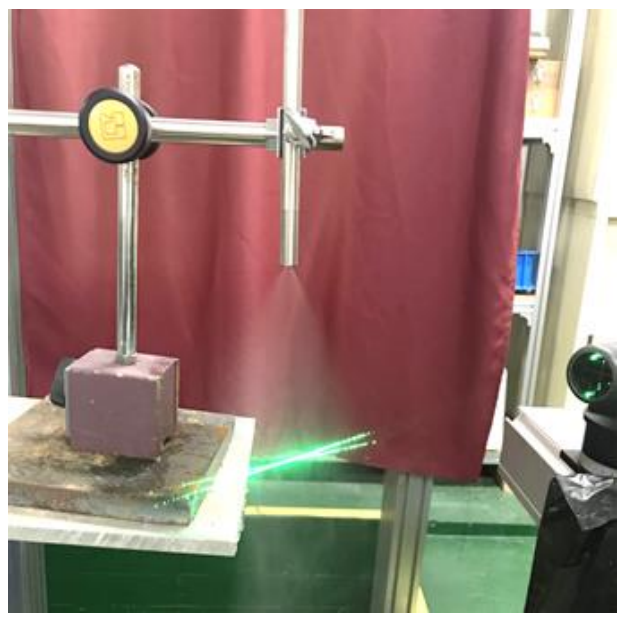

Figure 2-8. The particle size measurement with Particle Dynamics Analysis

Two laser are projected cross to counter and measure each particle rapidly. Particle size was measured 12 cm away from the orifice. The analysis was performed at *Korea Institute of Machinery & Materials*

2.2.2 Distribution Comparison with Methylene Blue Solution

Distribution comparison between using nozzle alone and using conical pendulum motion device was performed by measuring spraying area with methylene blue solution. When using nozzle alone, the nozzle was set perpendicular to a carton paper by a clamp. The distance between the orifice and a carton paper is same as granulometric analysis,12cm. When using conical pendulum motion device, the motor box was placed vertically to a carton paper so that the nozzle and vertical line made 30 degrees. The distance between the orifice and a carton paper is also 12cm vertically. 30ml of methylene blue solution was sprayed at 30ml/min in both experiment. Area measurements were conducted 5 times to obtain a mean value respectively.

2.2.3 Ex-vivo Penetration Depth Analysis

A 3.5L hermetic plastic box was used to mimic the abdomen. 12mm and 5mm trocars (TR12F, TR05F, DalimSurgNET Co., Ltd, Korea) were inserted in the cover of the plastic box, and the gaps were completely sealed. The nozzle and temperature/humidity sensor (ETH-01D, Econarae, Korea) were inserted in 12mm, 5mm trocars respectively. Temperature (℃) and humidity (%) were displayed via a 16x2 character dot-matrix LCD module.

CO2 supply(Insufflator) was connected to the 5mm trocar to maintain the pressure of 12 mmHg in the hermetic plastic box and the temperature of the plastic box was kept at 36℃ to simulate the environment of the abdomen during the PIPAC procedure.

Three different plastic boxes and tissue samples were prepared prior to the experiment to study the effect of varying nozzle positions on the penetration depth. The investigated distances between the nozzle and the tissue were 2, 4, and 8cm. For each group, a tissue sample was placed on the opposite side of the nozzle tip and sprayed with doxorubicin of chemotherapeutic drugs. Doxorubicin is one of chemotherapeutic drugs that is being used prevalent. Some chemotherapeutic agents including doxorubicin are approved for intraperitoneal use, so that regulatory framework conditions are rather favorable.

After spraying 50 ml of NaCl 0.9% containing 3 mg of doxorubicin at 36℃ of temperature, the tissue sample remained in the box for 30 minutes while maintaining the same pressure and temperature that whole procedure is almost same as current PIPAC treatment.

After 30 minutes, the insufflator was turned off. Vacuum system was operated with 1um pore-sized filter.

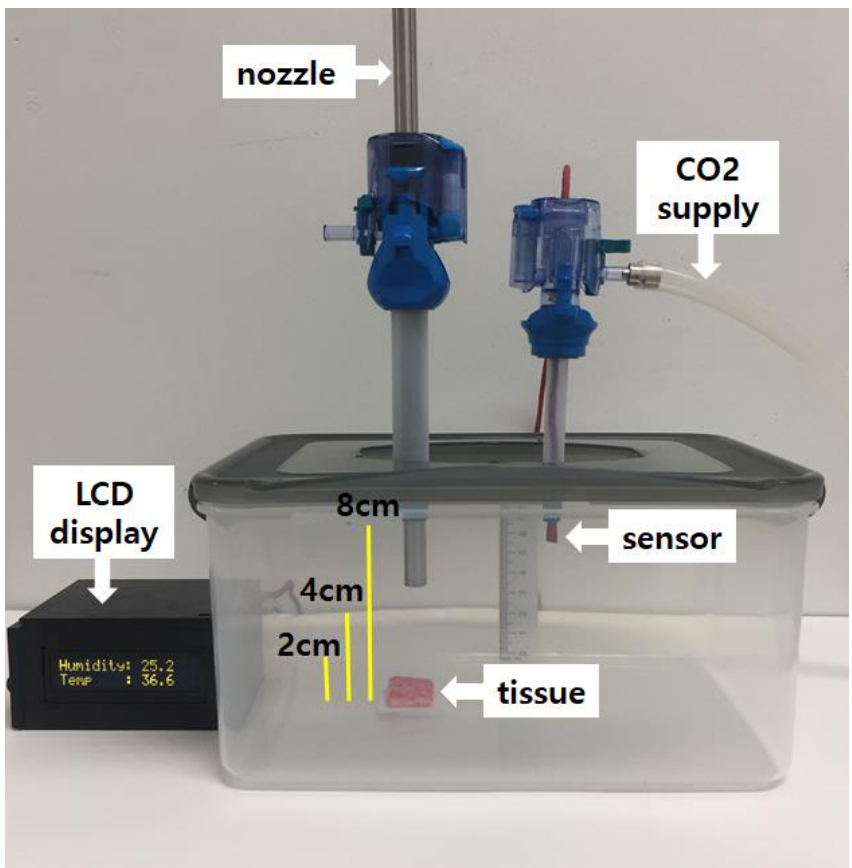

Figure 2-9. Ex-vivo penetration depth experiment

Laparoscopy-like ex vivo with fresh swine peritoneum was performed under the same condition as the PIPAC treatment at the temperature of 36℃ and pressure of 12mmHg. To investigate the penetration depth with different nozzle level of 2, 4, 8 cm, doxorubicin was sprayed by our nozzle and syringe pump.

2.2.3.1 Confocal Microscopy Analysis

After completion of PIPAC using doxorubicin, all the tissue samples were rinsed with NaCl 0.9% saline to remove superficial cytostatics, and then immediately frozen in liquid nitrogen tank. Cryosections of 7 um were prepared from three different areas of each tissue, which were mounted with VectaShield containing 1.5 ug/ml of 40,6-diamidino-2-phenylindole (DAPI) to stain cell nuclei. The penetration of doxorubicin into the tissue was measured by a Leica TCS SP8 confocal laser scanning microscope with immersion oil. In the current study, it was defined depth of concentrated diffusion (DCD) as the distance between the luminal surface and the inner most positive staining for doxorubicin accumulation, and depth of maximal diffusion (DMD) as the distance between the luminal surface and the furthest distance showing the extreme positive staining from the luminal surface.

2.2.3.2 Statistical test

For comparing DCD and DMD at the three different nozzle levels of 2, 4, 8 cm, a total of three tissue sections per tissue sample were subjected to the measurement of doxorubicin penetration, and Kruskal Wallis test was performed. For statistical analyses, SPSS software version 22.0 (IBM, Armonk, NY, USA) was used, and P value of <0.05 was considered to be statistically significant.

2.3 PIPAC Performance Test

2.3.1 In-vivo Distribution Comparison with Methylene Blue Solution

The Institutional Animal Care and Use Committee (IACUC) board at Seoul National University Hospital approved the current study, and then four swine from 45 to 50 kg were operated under general anesthesia using the following protocol. After making the condition of pneumoperitoneum of 12 mmHg using a Veress needle, 5-mm and 12-mm trocars were inserted into the abdomen for two swine. After performing general exploration using 5-mm laparoscopic camera, the nozzle was inserted into the 12-mm trocar. Thereafter, methylene blue (5 ml) diluted into 50 ml of 0.9% NaCl was nebulized at room temperature (23 ℃) into the abdominal cavity, and an intra-abdominal pressure of 12 mmHg maintained for 30 minutes. In the other two swine, the same concentrated amount of methylene blue was nebulized using conical pendulum motion.

2.3.2 In-vivo Penetration Depth Analysis without Conical Pendulum Motion Device

For three swine from 45 to 50 kg swine, 50 ml of NaCl 0.9% containing 3 mg of doxorubicin was nebulized with 30 ml/min using nozzle alone at room temperature, and then intra-abdominal pressure of 12 mmHg maintained for 30 minutes. Thereafter peritoneal or serosa tissues from 11 regions were obtained (Figure 2-10), which were rinsed with NaCl 0.9% saline to remove superficial cytostatics and immediately frozen in liquid nitrogen tank. Cryosections of 7um were

prepared from three different areas of each tissue, which were mounted with DAPI to stain cell nuclei. DCD and DMD were measured by a Leica TCS SP8 confocal laser scanning microscope with immersion oil.

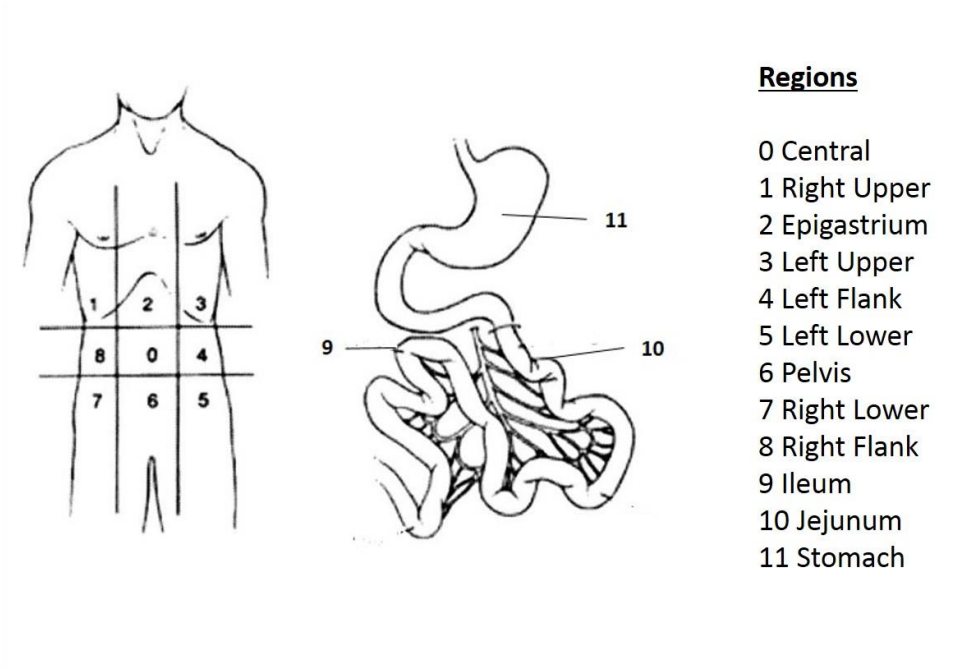

Figure 2-10. Twelve regions for evaluating penetration depth of doxorubicin after PIPAC

2.3.3 In-vivo Penetration Depth Analysis with a Conical Pendulum Motion Device

The same procedure was performed using a conical pendulum motion device for three swine from 45 to 50 kg for evaluating its impact to improving DCD and DMD.

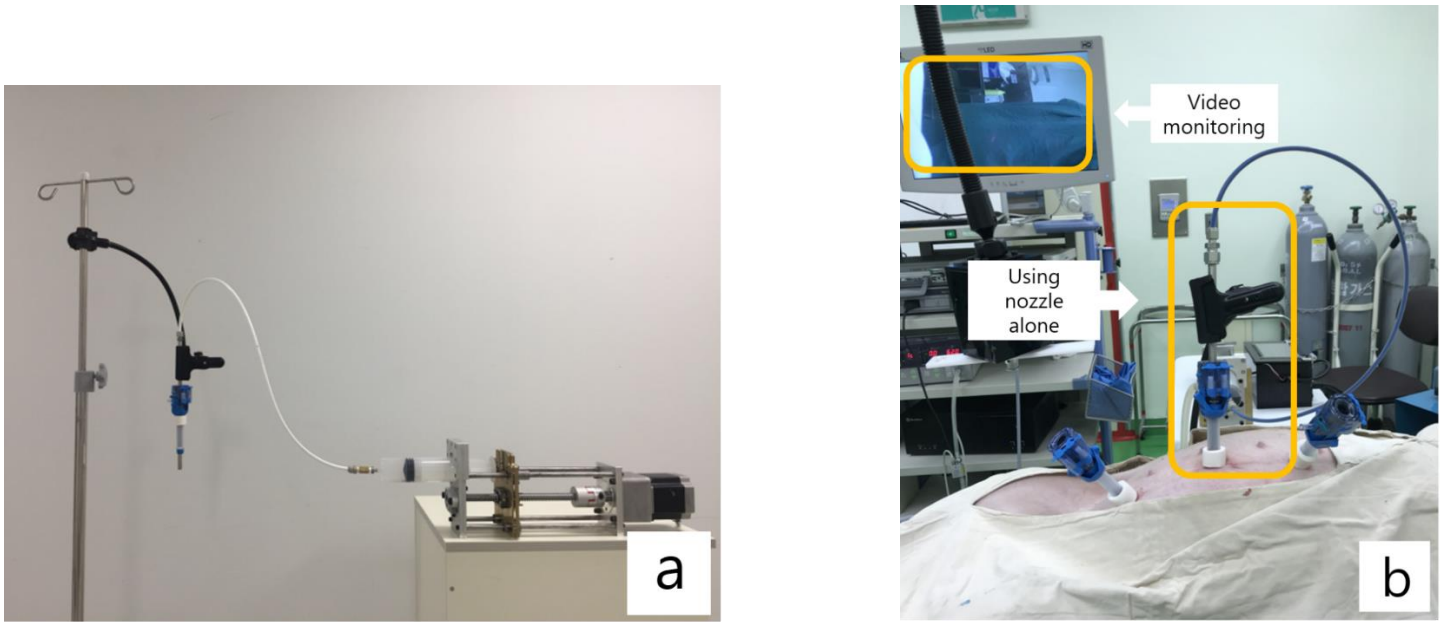

Figure 2-11. In-vivo experiment with using nozzle alone

Figure 2-11 (a) shows the PIPAC equipment of using nozzle alone, and (b) is a picture of a PIPAC surgery set up performed in a swine model during laparoscopy. A video monitor was set up to view the peritoneal cavity during the PIPAC procedure. Goose neck clamp is used to grasp the nozzle during the procedure.

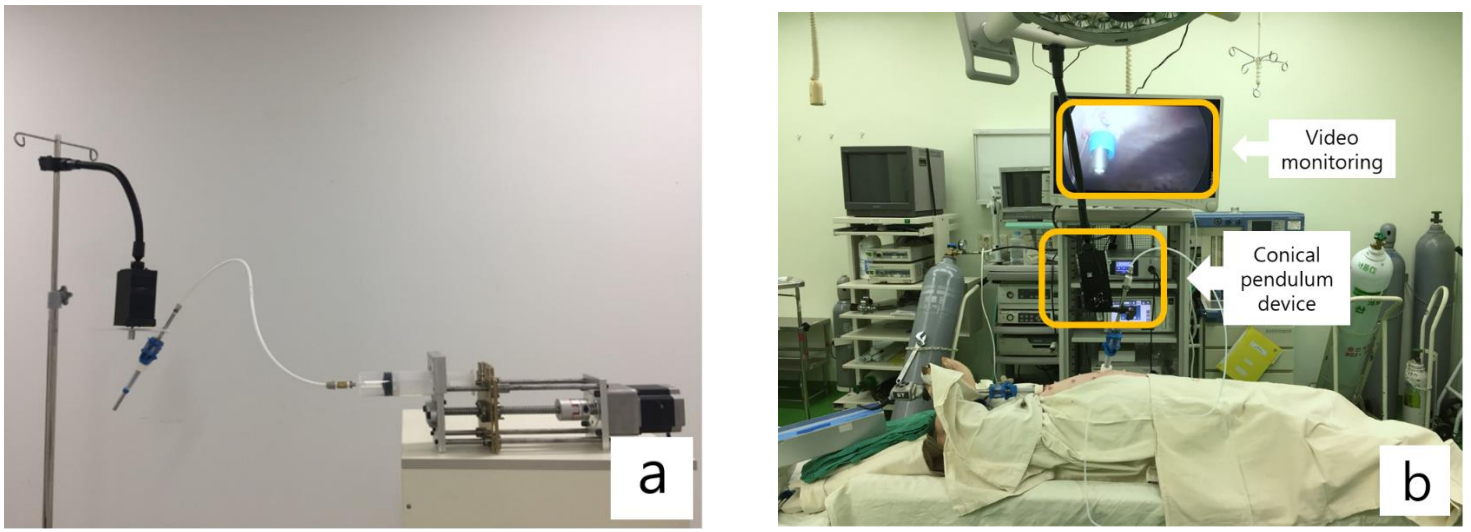

Figure 2-12. In-vivo experiment with using conical pendulum motion device

Figure 2-12 (a) shows the PIPAC equipment of conical pendulum motion device, and (b) is a picture of a PIPAC surgery set up performed in a swine model during laparoscopy. A video monitor was set up to view the peritoneal cavity during the PIPAC procedure. Contrary to Figure 2-11, our nozzle was inserted to the device that rotates to move like conical pendulum motion.

Chapter 3. Results

3.1. Nozzle Performance Test

3.1.1 Granulometric Analysis and Spray Angle Analysis

The granulometric analysis was performed with the average of 8168 of particles. The distribution of particle sizes is shown in Figure 3-1. The x-axis is the range of particle sizes, and the y-axis is the number of particles assigned to the corresponding range. It was observed as two types of mean diameter measurements, Arithmetic mean diameter and Sauter mean diameter, to test the nozzle performance. The Sauter mean diameter measurement is widely used to characterize a nozzle. Arithmetic mean diameter obtained from equation (1) is the average of the diameters of all the particles, and Sauter mean diameter from equation (2) is obtained from the volume to surface ratio. The Arithmetic and Sauter mean diameters of our nozzle were 25.4μm and 32.1μm, respectively as shown in Table 1. The mean particle velocity from the nozzle was calculated as 1.31m/s. The calculated spray angle was 77.2° with a flow rate of 30 ml/min.

$$D_{10} = \frac{1}{N}\sum^{N} n_i D_i \quad \cdots\cdots \quad (1)$$

$$D_{32} = \sum^{N} n_i {D_i}^3 \Big/ \sum^{N} n_i {D_i}^2 \quad \cdots\cdots \quad (2)$$

Flow rate (ml/min)	Height (mm)	Mean Particle velocity (m/s)	Mean diameter(μm)	
			Arithmetic Mean Diameter (μm)	Sauter Mean Diameter (μm)
30	120	1.31	25.4	32.1

Table 1. Granulometric analysis results

The values of Mean particle velocity and Mean diameter (Arithmetic mean diameter and Sauter mean diameter) measured at 30 ml/min of flow rate and 12 cm of height from laser to an orifice of the nozzle

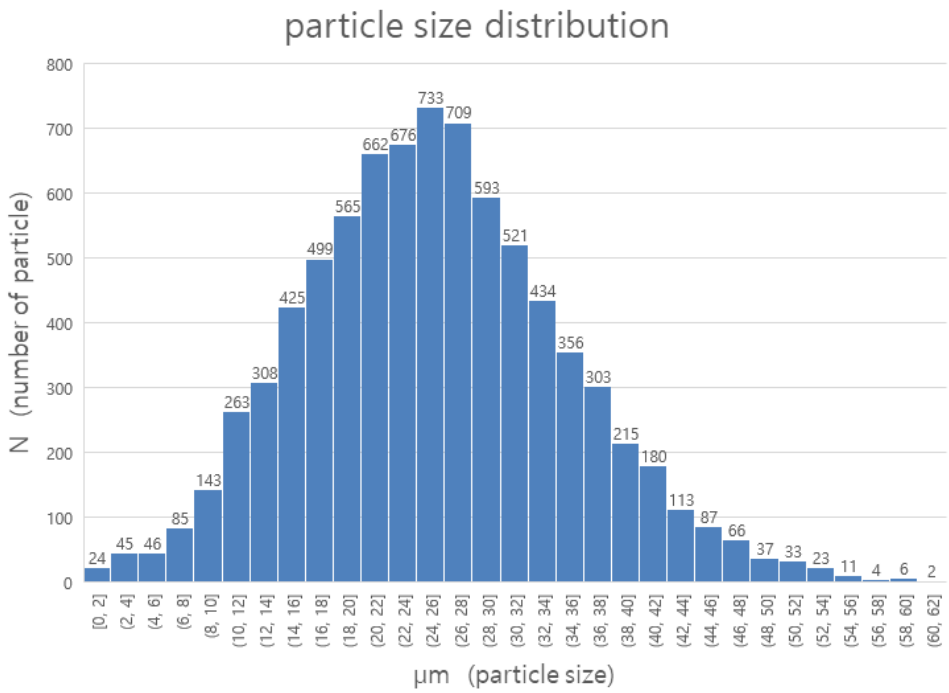

Figure 3-1. Particle size distribution

Granulometric analysis performed for the nozzle prototype shows the particle size distribution and a corresponding number of particles. The number of 8168 of particles were inspected to measure the particle size and particle velocity.

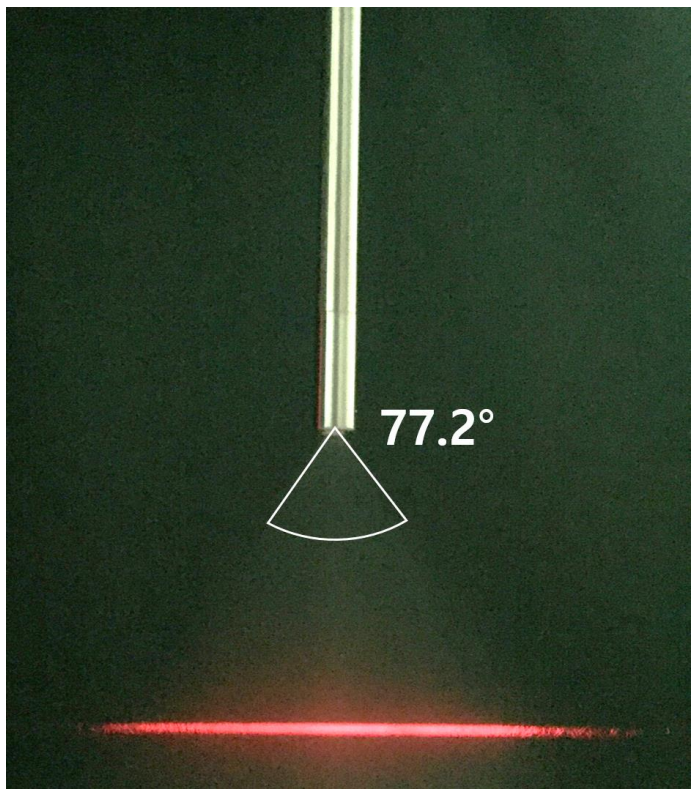

Figure 3-2. The side view to measure the spray angle

The laser is projected 12 cm apart from the orifice. The laser path is only shown where it interacts with the sprayed particles.

3.1.2 Distribution Comparison with Methylene Blue Solution

Both methods, using nozzle alone and using conical pendulum motion device, show similar distribution characteristics. The area with dye is divided by two parts; concentrated zone and a spread zone in both methods. The concentrated zone is the area where the methylene blue solution is sprayed intensively while the spread zone is where the solution is sprayed with less intensity. However, the distributed area which is sprayed by conical pendulum motion device is evidently larger than the area sprayed with nozzle alone.

The diameter of the two areas were measured five times each to obtain the average value. The average diameter of the concentrated zone obtained from the nozzle alone is 18.5±1.2cm, which is wider than the nebulizer' distribution area which is used in previous study[15], and the average diameter of the spread zone is 28.3±1.6cm.

The average diameter of the concentrated zone obtained from the conical pendulum motion system is 34.7±2.4cm which is approximately twice that from the nozzle alone. The average diameter of the spread zone is 42.4±2.5cm that is more than third the diameter of the concentrated zone from nozzle alone.

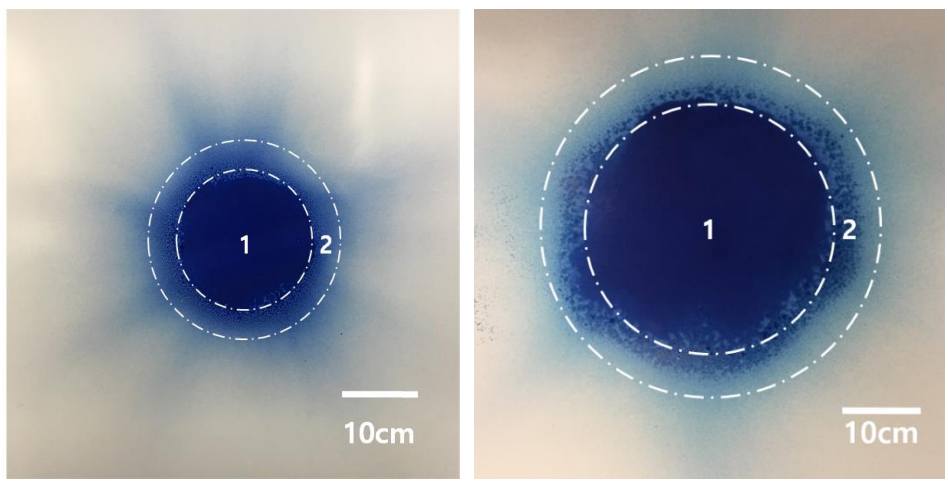

Figure 3-3. Methylene blue solution distribution comparison

30ml of the dye is sprayed 12cm away from a carton paper at a flow rate of 30ml/min. Left figure is distribution of using nozzle alone; Right figure is distribution of using conical pendulum device. In both experiment, 1 is the concentrated zone with intense particle distribution, and 2 is the spread zone where it shows a sparse distribution pattern.

3.1.3 Ex-vivo Penetration Depth Analysis

Figures 3-4 shows results of confocal microscopy analysis for evaluating DCD and DMD of doxorubicin in the three tissues 2, 4 and 8 cm away from the nozzle. The mean values of DCD at nozzle positions of 2, 4 and 8cm were 255.3±4.5, 251.7±9.5, and 253.1±5.3 um ($p>0.05$), respectively, showing no difference of DCD among the three positions (Figure 3-5). However, the mean values of DMD were 515.3±5.7um, 437.6±3.6um and 363.2±7.4um at 2, 4, 8cm, respectively ($p<0.05$), suggesting the closer the distance from the nozzle to the tissue, the more significant DMD increase (Figure 3-6).

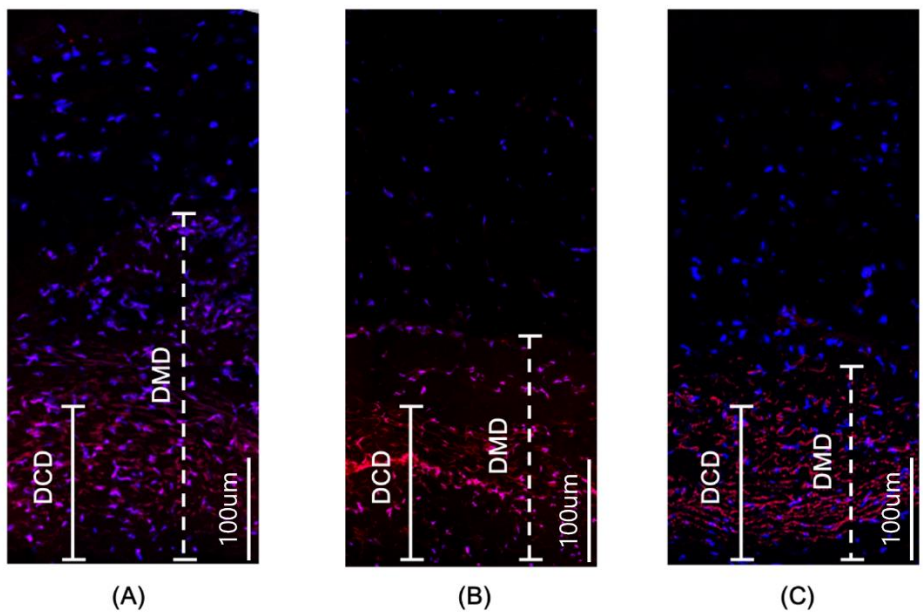

Figure 3-4. Confocal microscopy analysis

Confocal microscopy analysis of maximal penetration depth(DMD) and concentrated penetration depth(DCD) of doxorubicin into fresh swine peritoneal tissue samples in ex-vivo experiment. Nuclei(red) were dyed with 4',6-diamidino-2-phenylindole (DAPI). Doxorubicin concentration(3mg/50ml). Left side to right: A = 2 cm, B = 4 cm, C = 8 cm.

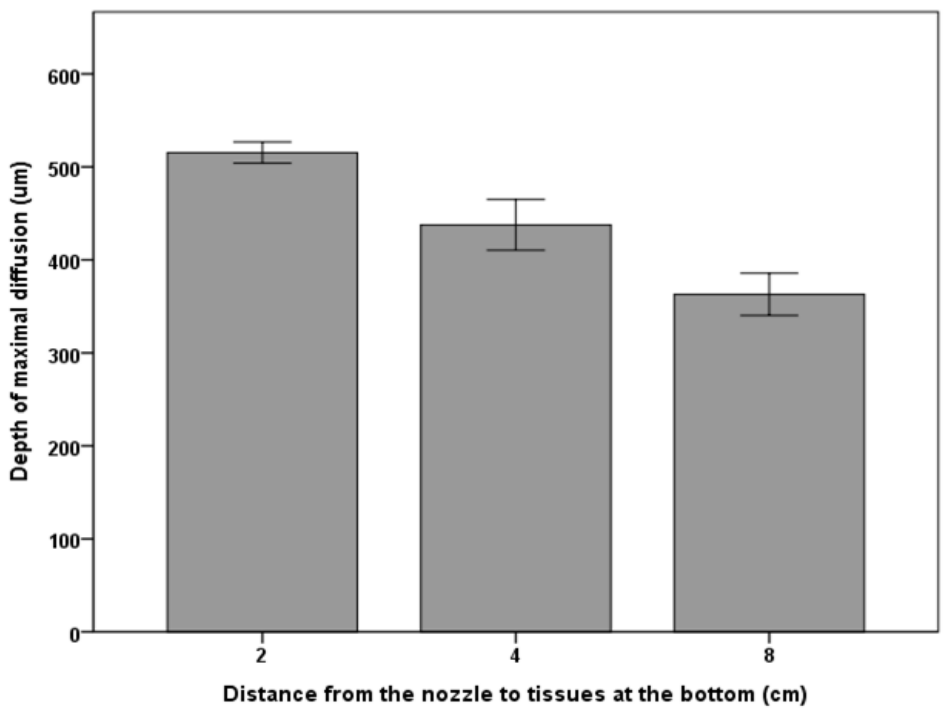

Figure 3-5. The mean depth of maximal diffusion(DMD) values of doxorubicin

The mean DMD values at nozzle positions of 2, 4, 8 were 515.3±5.7um, 437.6±3.6um, and 363.2±7.4um and significant differences were shown among all groups (2cm vs 4cm, 2cm vs 8cm, and 4cm vs 8 cm, $p<0.05$).

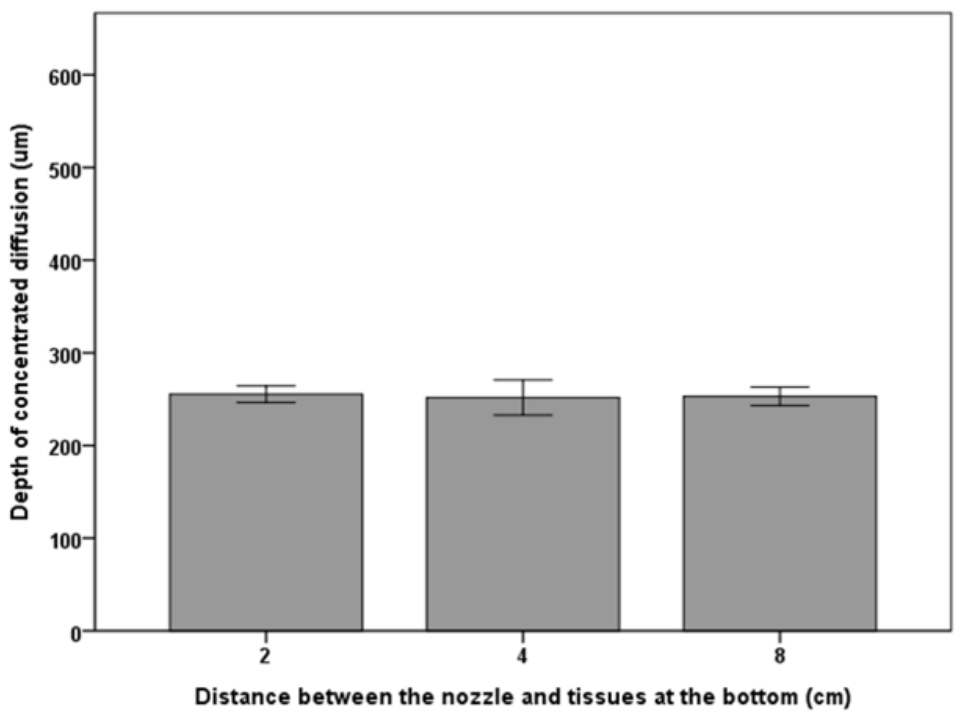

Figure 3-6. The depth of concentrated diffusion(DCD) values of doxorubicin

The mean DCD values at nozzle positions of 2, 4 and 8cm were 255.3±4.5, 251.7±9.5, and 253.1±5.3 um and no significant differences were observed ($p>0.05$).

3.2 PIPAC Performance Test

3.2.1 In-vivo Distribution Comparison with Methylene Blue Solution

Figure 3-7 shows the result of In-vivo distribution of methylene blue nebulized. After PIPAC procedure, clinicians opened the abdomen and compared the distribution of methylene blue between nozzle alone and conical pendulum motion in whole abdominal cavity, diaphragm, small bowel, liver, gall bladder and stomach. As a result, it was observed that methylene blue was more strongly and widely colored in a swine treated with PIPAC using conical pendulum motion.

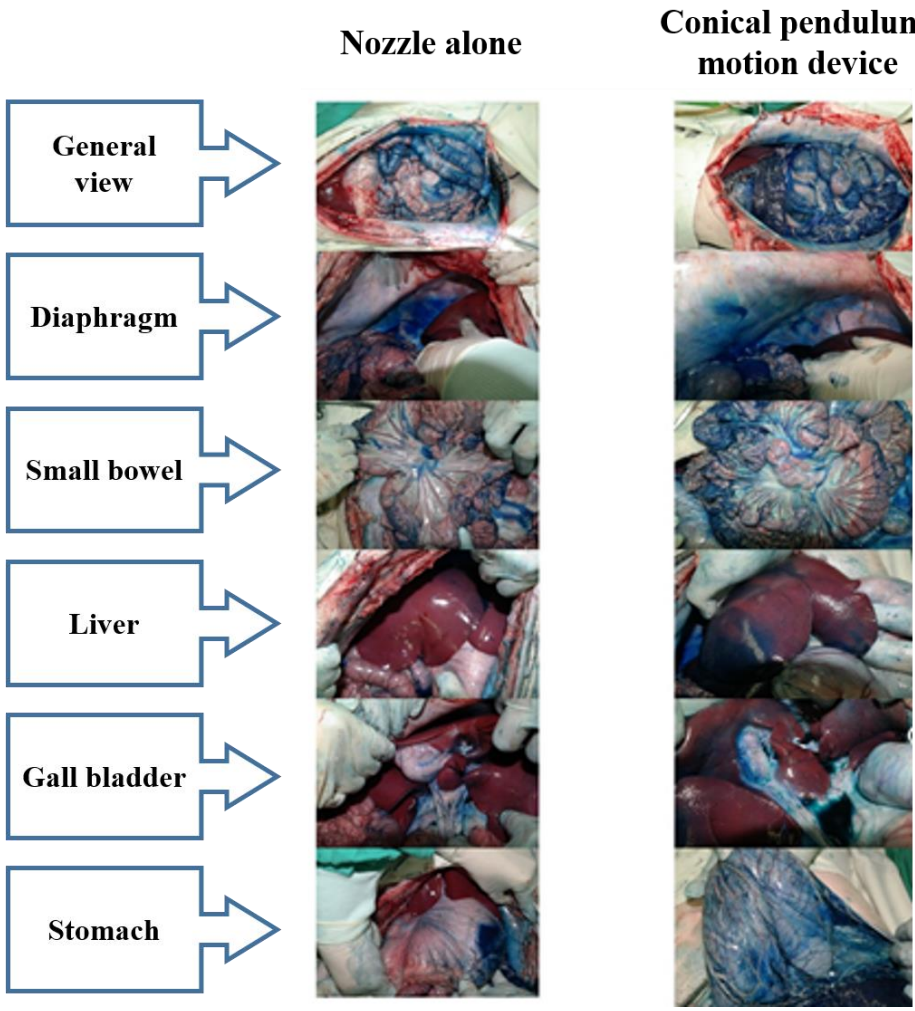

Figure 3-7. Comparison of Methylene Blue Solution Distribution

Figure 3-7 shows the comparison of dye distribution at in-vivo experiment. From the top, the comparison pictures of general view, diaphragm, small bowel, liver, gall bladder, stomach are displayed. Especially, there are significant differences at liver and stomach when using conical pendulum motion device rather than using nozzle alone.

3.2.2 In-vivo Penetration Depth Analysis

Figure 3-8 shows the results of comparison of DCD and DMD after PIPAC between nozzle alone and conical pendulum motion. In terms of DCD, the mean values with standard deviation between nozzle alone and conical pendulum motion were 194.3±7.51um vs. 225±7um, 238±19.3um vs. 262±21.8um, 203.7±3.2um vs. 315.7±6.7um, 215.7±27.4um vs. 236.3±7.4um, 363.7±64.8um vs. 371.7±55.8um, 252.7±30.7um vs. 299±27.9um, 217±13.2um vs.252.7±22.1um, 170±13.5um vs. 209.3±10.1um, 196.7±26.5um vs. 238.3±22um, 729.3±24.7um vs. 869±70.5um, 0um vs. 0um, 347.7±59.3um vs. 443.7±26.6um in central, right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank, ileum, jejunum and stomach regions. Among all regions, DCD increased with conical pendulum motion in central, epigastrium, left lower, pelvis, right lower, ileum and stomach regions, when compared with nozzle alone.

Moreover, the mean values of DMD with standard deviation between nozzle alone and conical pendulum motion were 247±20.1um vs. 348.7±25.1um, 282.3±24um vs. 331±37.5um, 272±26.7um vs. 401.7±5.5um, 278.3±8.5um vs. 331±25.5um, 482±37.4um vs. 613.3±31um, 382.3±22.7um vs. 445.3±49.6um, 331.7±23.1um vs. 395.3±14.5um, 245±26.8um vs. 322.3±36.7um, 311.3±43.4um vs. 329.7±11.7um, 1122±64.6um vs. 1275.7±61um, 0 um vs. 0 um () and 491.3±24.6um vs. 676.7±51.1um in central, right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank, ileum, jejunum and stomach regions. In particular, DMD also increased with conical pendulum motion in central, epigastrium, left upper, left flank, pelvis, right lower, ileum and stomach regions in comparison with nozzle alone.

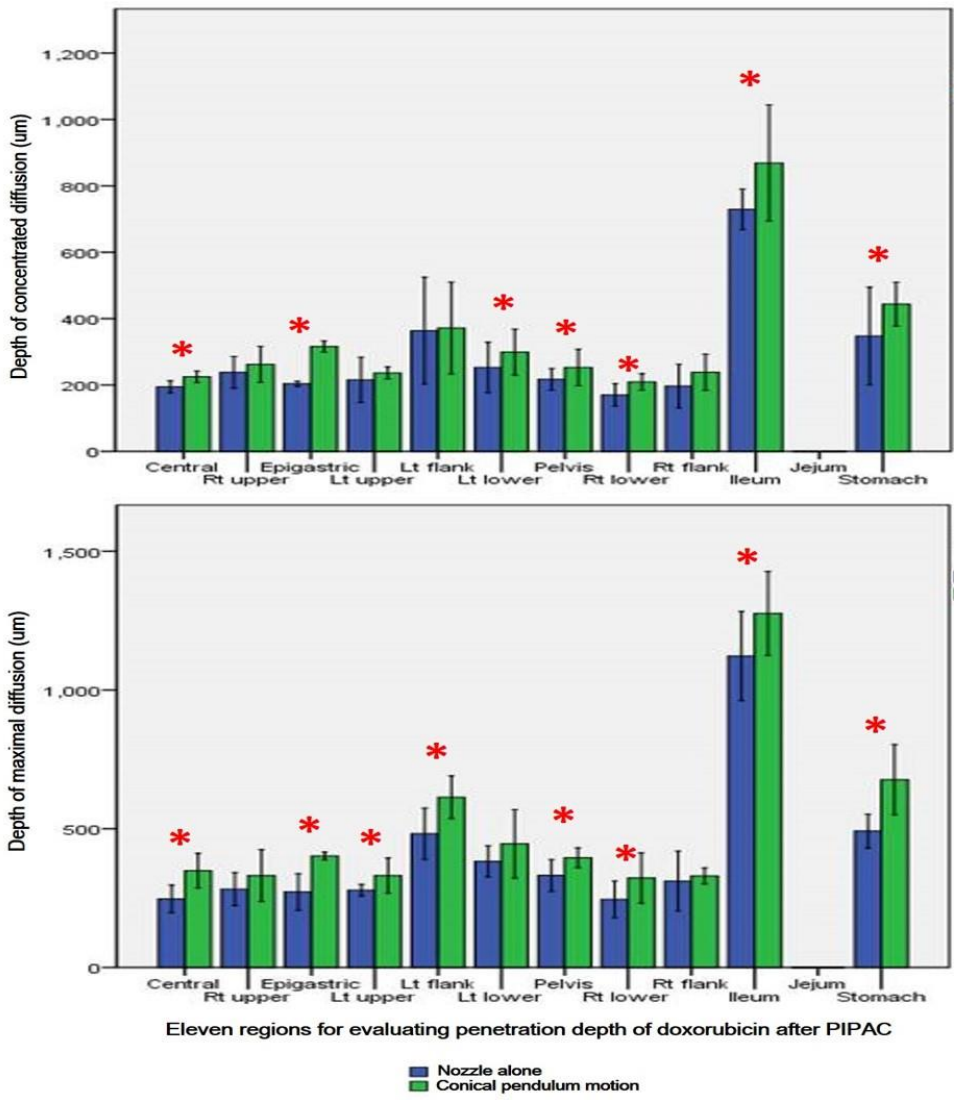

Figure 3-8. Comparison of depth of concentrated diffusion (DCD) and depth of maximal diffusion (DMD) after PIPAC between nozzle alone and conical pendulum motion

Chapter 4. Discussion

PIPAC has been offered as a new approach for PC treatment due to its promising outcomes overcoming the limitations of conventional chemotherapy treatment and intraperitoneal chemotherapy. It has demonstrated better drug efficacy and ameliorated the systemic effect of chemotherapy by delivering a significantly lower dose and concentration of drugs directly to the locational tumor tissues. Despite these advantages, PIPAC needs to overcome a significant limitation regarding its drug distribution area as the current PIPAC devices do not guarantee homogenous drug distribution across the peritoneal cavity.

For the optimization of PIPAC treatment, therefore, studies have been investigated and developed to make a novel PIPAC system with a conical pendulum motion device. The performance of nozzle using our prototype is comparable to that of MIP, the current PIPAC system.

4.1 Effective Penetration Depth and Drug Distribution with Lower Pressure

The prototype was designed to spray around 30um drug droplets at a flow rate of 30ml/min. The particle size was chosen to be larger than the aerosol size from nebulizer systems to reduce the probability of chemotherapeutic drug leakage and thereby improving the safety aspect for clinicians.

The current PIPAC system produces the average particle size of 20um with a pressure range up to 20 bars[15]. However, the prototype used in this study generates the average particle size of 32um using the pressure up to 7 bars. This demonstrates that our prototype produces targeted particle with a significantly lower pressure.

The distribution area of the PIPAC system was also evaluated. It was observed as the distribution area of the PIPAC system with our prototype using the same methylene blue solution used in previous studies[15]. Comparing the distribution areas of our prototype and current PIPAC system, our device demonstrated wider dyed area at a shorter distance than the other. Moreover, using conical pendulum motion device, this would show a significantly wider drug distribution area in the peritoneal cavity.

4.2 Comparable Penetration Depth

Previous studies[3, 16] have shown that limitations exist in drug distribution with current PIPAC devices. In ex-vivo experiments, tissue penetration depths in the Wall, Top, and Bottom covered presented significantly insufficient results than that in the tissue placed directly below the nozzle. As non-homogenous distribution patterns with the PIPAC devices had already been demonstrated in the studies, an ex-vivo experiment was performed under the same conditions only with tissue placed directly below the nozzle at varying nozzle levels to investigate the effect of nozzle height on penetration depth. Penetration depth was examined through the DAPI analysis.

As the results show, the mean DMD values were significantly different among the investigated nozzle positions. Also the mean DMD values obtained from our prototype also demonstrated comparable performance as the reported penetration depths from MIP at all nozzle positions of 2, 4, and 8cm[16]. While MIP obtained this result with 20 bars of applied pressure, our prototype achieved it with only 7

bars. This result suggests that the current PIPAC technology can be significantly improved by reducing the amount of applied pressure from 20 bars to 7 bars to obtain a slightly improved penetration depth results.

4.3 Importance of Conical Pendulum Motion Device

Previous studies have only considered the maximum penetration depth[3, 16]. However, this study prioritized the mean DCD values since the zone that has concentrated population of stained cells is more likely to contribute to the lesion treatment rather than the maximum penetration depth where only a few cells are affected by the drug. As shown in the result, the DCD values demonstrated no significant differences at all levels of the nozzle. The similar DCD values reveal that the nozzle level is not an important factor that decides the penetration depth of the drug in PIPAC treatment. They also indicate that the area of tissue directly exposed to the sprayjet of the nozzle must be increased for a wider range of homogenous drug distribution while maintaining the same penetration depth. Therefore, these results prove the conical pendulum motion device that would affect wider range of lesion is needed.

PIPAC technology has been focused on aerosolizing the drug and reducing its particle size for homogenous distribution. However, PIPAC has faced technical limitations since smaller particle size requires higher pressure. Currently, Angio injectors are used in PIPAC to generate up to 20 bars of pressure to spray 20um drug particles through the nozzle. In order to overcome the current limitation, a device that can produce higher pressure than 20 bars must be developed. Producing pressure larger than 20 bars, however, would require an unstable system that would require a huge amount of time, expense and space. Therefore, the focus should remain on

increasing the area of tissue directly exposed to the jet stream of the nozzle rather than decreasing the particle size.

4.4 Notable results in In-vivo experiments

This study found that our PIPAC system may have comparable efficacy for drug diffusion and penetration, and rotation of nozzle using conical pendulum motion increased the efficacy in In-vivo model. In terms of distribution using methylene blue, stained areas are wider and color intensity was stronger when using conical pendulum motion. Moreover, penetration depth of doxorubicin increased in most of peritoneal areas by conical pendulum motion, which suggests that drug response can be expected to increase with conical pendulum motion. However, there is a limitation that aerosol could not be delivered in some areas blocked by other organs (ex. jejunum).

4.5 Limitations of the Present Study

Our nozzle which is used in this study shows a notable performance than previous studies which is related to PIPAC treatment and conical pendulum motion device has a remarkable ability to spray drugs with wide range. However, our system has a few limitations that are unable to be overcome in the present study.

Firstly, there is a problem which is related to the remaining drugs. After spraying drugs, there is 20ml volume of drugs between syringe and the orifice. To inject the rest of drugs, the other liquid must be injected after spraying chemotherapeutic drugs. But in this way, the concentration of drugs could be changed and it could be affected to the patient in negative. Instead of other liquid, air could be injected after spraying chemotherapeutic drugs. However, the power which is made by air is significantly

different rather than made by liquid. It means the nozzle cannot be affected with approximately pressure so that it is hard to generate suitable particle size of drugs. Therefore, methods are still investigated to reduce the remaining drugs by decreasing the inner volume of nozzle or using other tubes whose inner diameter is smaller and also which can endure the high pressure.

Secondly, conical pendulum motion device cannot be controlled remotely while the syringe pump can be operated by remote controller. Spraying chemotherapeutic drugs process is performed only 5 minutes. So conical pendulum motion device is operated during spraying process. It does not need to be operated after finishing spraying. If conical pendulum motion device is worked during 30 minutes unnecessarily in whole PIPAC treatment procedure, it has a distinct possibility that the operative region which is made during laparoscopy could be loosen and aerosolized drugs could be leaked out of peritoneal cavity.

Chapter 5. Conclusion

In this study, a novel pressurized intraperitoneal aerosol chemotherapy(PIPAC) system with a conical pendulum motion device is introduced.

Three components have been developed; Nozzle, High pressure syringe pump, Conical pendulum motion device. Through nozzle performance test, the nozzle is proved as a wider distribution ability than current nozzle which is being used in current PIPAC system. Moreover, in the aspect of penetration depth, our nozzle performance is comparable to Micropump. However, it has been focused on the concentrated penetration zones which are actually effective to tissues and those are quite similar as different levels of nozzle. It has been demonstrated that the distance between the nozzle and tissues is not significantly important factor.

Instead of efforts to reduce the drug's particle size, a method has been developed to spray drugs with a wider range intuitively by applying conical pendulum motion. Ultimately it is proved that using conical pendulum motion device with our nozzle affects a wider area in peritoneal cavity by in-vivo experiment.

A method has been currently investigated to eliminate limitations of our PIPAC system. Also, in-vivo tests have been performed to prove our PIPAC system with a variety of chemotherapeutic drugs.

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국문 초록

원뿔 진자 운동 기기를 이용한 고압 복강 에어로졸 항암화학요법 시스템 개발

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대장암과 난소암은 예후가 불량하여 재발 가능성이 높은 대표적인 골반 종양이다. 이러한 골반 종양들은 재발 과정에서 복강 파종을 보인다. 조기 진단이 쉽지 않고, 생존율이 다른 암들에 비해 낮으며 치료법이 다양하지 않기 때문에 복강 파종이 진행되고 있는 환자는 말기 암환자로 간주한다.

대장암과 난소암의 치료를 위해서 직접 복강 내에 항암제를 투여하는 세척복강항암화학요법(LIPEC)과 고온복강항암화학요법(HIPEC)과 같은 새로운 치료법이 도입되었다. 위 치료들은 정맥주사 항암화학요법의 부작용들을 줄일 수 있는 장점을 보이나 여러가지 단점이 있다. 먼저 조직 내의 약물 침투 깊이에 한계가 있고, 복강 내에 약물을 골고루

분포 시킬 수 없다는 단점을 보인다. 또한 신부전 등을 포함한 중증의 합병증을 일으킬 수 있 수도 있다.

그에 따라 유럽을 중심으로 한 고압 복강 에어로졸 항암화학요법(PIPAC)이 복강 파종의 새로운 해결책으로 대두되고 있으며 현재 전임상 시험을 거쳐 임상 시험에 돌입한 상태이다. 복강경 수술을 통해 항암제를 에어로졸 형태로 복강에 분사한 후 복강 안을 12mmHg 의 고압 상태로 30 분간 유지하여 약물의 침투 효과를 향상 시키는 새로운 치료법이다. 정맥 주사 항암제 용량의 10%, HIPEC 에서의 20%를 사용하고 고온으로 인한 합병증이 거의 발생하지 않아 반복적으로 치료할 수 있다는 장점이 있다. 하지만 이 또한 복강 내에서 약물이 균일하게 본포 되지 못하는 단점을 가지고 있다. 본 연구에서는 현재 치료법들의 단점들을 극복하기 위하여 '원뿔 진자 운동 기기를 이용한 고압복강에어로졸항암화학요법 시스템'을 개발하였다. 노즐, 고압용 시린지 펌프, 원뿔 진자 운동 기기를 제작하여 노즐 자체의 특성을 알아보는 다양한 실험을 진행하였고, PIPAC 으로써의 성능을 확인하기 위해 생체내 실험을 진행하였다. 그 결과, 본 연구에서 개발된 노즐과 고압용 시린지 펌프는 분사 넓이와 침투 깊이 측면에서 기존에 사용되고 있는 노즐보다 향상된 성능을 보이는 것을 확인할 수 있었으며, 원뿔 진자 운동 기기를 이용한 체내 실험에서도 노즐만 사용했을 때와 비교하여 더 넓은 장기에 유의미하게 영향을 끼친다는 것을 확인하여 항암 요법으로써 적용 가능성을 확인하여 향후 새로운 항암요법으로 발전할 수 있음을 시사한다.

주요어 : 복강 파종, 고온항암화학요법 (HIPEC),
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