외과학 석사 학위논문

온열 가압 복강내 에어로졸 항암치료의 개발에 대한 돼지 실험

Development of Hyperthermic Pressurized Intraperitoneal Aerosol Chemotherapy in a Porcine Model

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이 논문을 외과학 석사 학위논문으로 제출함

2015년 10월

서울대학교 대학원

의학과 외과학전공

정 도 현

정도현의 석사학위논문을 인준함

2015년 12월

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본인은 아래의 학위논문이 제3자의 권리를 침해하지 않았음을 서약하며, 서울대학교가 다음과 같이 저작물을 이용하는 것에 동의합니다.

논문 제목	온열 가압 복강내 에어로졸 항암치료의 개발에 대한 돼지 실험 Development of Hyperthermic Pressurized Intraperitoneal Aerosol Chemotherapy in a Porcine Model
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1. 본인은 서울대학교가 위 저작물을 인터넷 등 정보통신망을 통해 복제·전송·배포하는 것에 동의합니다.

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서울대학교총장 귀하

Abstract

Development of Hyperthermic Pressurized Intraperitoneal Aerosol Chemotherapy in a Porcine Model

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Background: Peritoneal carcinomatosis is an unmet therapeutic need. Several types of intraperitoneal chemotherapy have been introduced. However, hyperthermic intraperitoneal chemotherapy has limited drug distribution and poor peritoneal penetration. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) does not have the benefits of hyperthermia. We developed a device to apply hyperthermic PIPAC (H-PAC) and evaluated its safety in a porcine model.

Methods: The device for H-PAC consisted of a laparoscopic aerosol spray and a heater to create hyperthermic capnoperitoneum. We operated on five pigs for the development of the new device and on another five pigs as a survival model. After a pilot experiment of the survival model (Pig A), a hyperthermic pressurized intraperitoneal aerosol of indocyanine green was administered after insertion of three trocars (Pig B) and laparoscopy-assisted distal gastrectomy (LADG) (Pig C) without chemotherapeutic agents. After that, H-PAC with cisplatin was administered after insertion of three trocars (Pig D) and LADG (Pig E). Autopsies were performed on postoperative day 7.

Results: Median operation time was 85 min (80–110 min). Intraperitoneal temperature was constant for 1 h of H-PAC (38.7–41.0°C). All five pigs were healthy and survived for 7 days. Median weight loss was 0.2 kg. Autopsy tissues of stomach, peritoneum and jejunum were intact in all five pigs.

Conclusion: H-PAC was safe in a porcine model.

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keywords : Peritoneum-therapy, Chemotherapy, Aerosol, Pig, Pneumoperitoneum, Hyperthermia-induced, Laparoscopic surgery

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목 차

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I. Introduction

Peritoneal carcinomatosis is important because it is found in many patients with gastrointestinal or gynecological carcinoma. For example, in gastric cancer, peritoneal carcinomatosis is the most common type of first recurrence and the most common cause of death (1, 2). In addition, many patients with gastric cancer display risk factors for peritoneal carcinomatosis: serosa exposure, other organ invasion, cancer perforation, and positive peritoneal lavage cytology (3).

However, there are no definitive treatment guidelines for peritoneal carcinomatosis (4). Many treatment methods have been evaluated, including cytoreductive surgery (CRS), radiotherapy, systemic chemotherapy, intraperitoneal chemotherapy (IPC), and combination therapy, but no treatment method has exhibited superiority of effectiveness over the others.

Theoretically, compared to the systemic treatments, IPC can achieve greater drug exposure to the peritoneal nodules (5). Therefore, various types of IPC have been introduced and are differentiated according to temperature or timing of treatment: normothermic IPC, hyperthermic IPC (HIPEC), early postoperative IPC, and delayed postoperative IPC (6). Of these variations, administration of HIPEC following CRS has been shown to significantly improve survival of patients with peritoneal carcinomatosis of colorectal and gastric origin (7, 8).

However, HIPEC has two significant pharmacokinetic problems: limited penetration into peritoneal nodules and limited intraperitoneal drug distribution (9). To overcome these two limitations, Solass et al. developed pressurized intraperitoneal aerosol chemotherapy (PIPAC) (10, 11). The treatment method was shown to significantly improve distribution and penetration of methylene blue into the peritoneal cavity in a preclinical experiment (10). Subsequently, the group also demonstrated the safety and utility of PIPAC in human patients: low systemic exposure and high local concentration, respectively (11-13).

However, despite addressing the pharmacokinetic problems of HIPEC, PIPAC fails to incorporate the advantage of hyperthermia (6). Although hyperthermic aerosols could potentially provide the same antitumor effect as hyperthermia in HIPEC, such a method would have to overcome several technical hurdles. Most importantly, compared to hyperthermic liquids, hyperthermic gasses are more difficult to produce and maintain, because the temperatures of gasses can change easily and rapidly due to lower density.

We have developed a device for hyperthermic pressurized intraperitoneal aerosol chemotherapy (H-PAC), which uses the improved distribution and penetration of pressurized aerosol and the superior antitumor effect of hyperthermia. The aims of the present study were to develop a device that can produce hyperthermic gas and maintain its

temperature stably, and to evaluate the safety of H-PAC in a porcine model. The present preclinical study, to our knowledge, is the first study of H-PAC in a porcine model.

II. Materials and Methods

1. Development of New Device

The H-PAC device consisted of a laparoscopic aerosol spray and a heater to create hyperthermic capnoperitoneum. The laparoscopic aerosol spray was used to administer an aerosol containing chemotherapeutic agents and used carbon dioxide (CO_2) gas, which is commonly used in laparoscopic surgery (Fig. 1).

The apparatus for hyperthermic capnoperitoneum consisted of heating units that increased the temperature of CO_2 gas, a CO_2 gas delivery line covered with a heating line, and a temperature monitor unit (WooGun ENG, Gyeonggi-do, Korea; Fig. 2a). The heating units heated the water to 52°C, and the CO_2 gas was heated to 37.5°C by passing through the heated water. The heating line that covered the CO_2 gas delivery has the most important role in maintaining the temperature of the CO_2 because otherwise, the CO_2 gas will lose heat easily and rapidly during delivery from the device to the porcine model (Fig. 2b). The heating line prevented cooling of the CO_2 gas during delivery and even increased the temperature of the CO_2 gas from 37.5 to 40°C. Lastly, a temperature-monitoring unit was located at the outflow pipe of the heating units where the CO_2 gas delivery line was connected to the heating units (Fig. 2c).

Figure 1. Laparoscopic aerosol spray

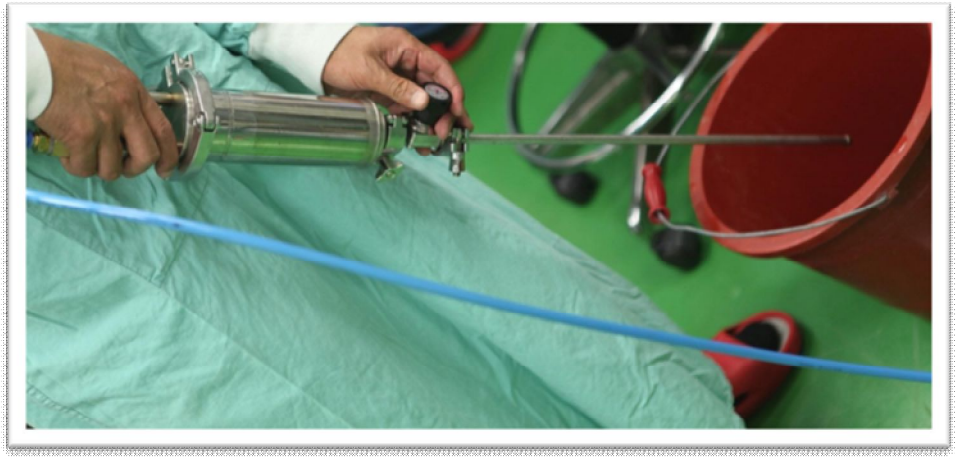
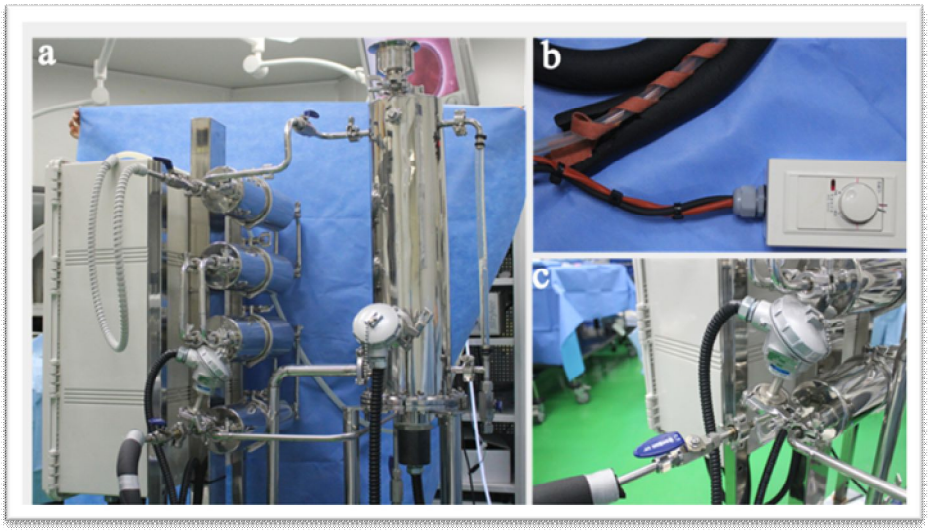


Figure 2.

(a) A heater to create hyperthermic capnoperitoneum

(b) A CO_2 gas delivery line covered with a heating line

(c) A temperature-monitoring unit was located at the outflow pipe of the heating units where the CO_2 gas delivery line connected to the heating units.



2. *Animals*

After receiving authorization from the Institutional Animal Care and Use Committee (IACUC; No. BA1408-159/044-01), we operated on five pigs for development of the new device and on another five pigs as a survival model, to evaluate the safety of laparoscopy-assisted distal gastrectomy (LADG) followed by H-PAC. All pigs were females and weighed 35–40 kg.

3. *Experimental Protocol 1: In vivo Test of New Device*

In the five pigs used for device development, three trocars were inserted under a pneumoperitoneum of 12 mmHg (Fig. 3a). The laparoscope was inserted through the first 12-mm trocar, which was located beneath the umbilicus, and hyperthermic CO_2 gas was infused through the first trocar (Fig. 3b). After exploration of the intra-abdominal cavity, the laparoscope was moved to the second 12-mm trocar, which was located at the right upper abdomen, and circulating CO_2 gas was extracted through the second trocar. A laparoscopic aerosol spray was administered through the first trocar to spray the entire intraperitoneal cavity because the trocar was located at the center of the abdomen (Fig. 3c). For the laparoscopic aerosol spray, we decided that the appropriate amount of solution (diluted ICG

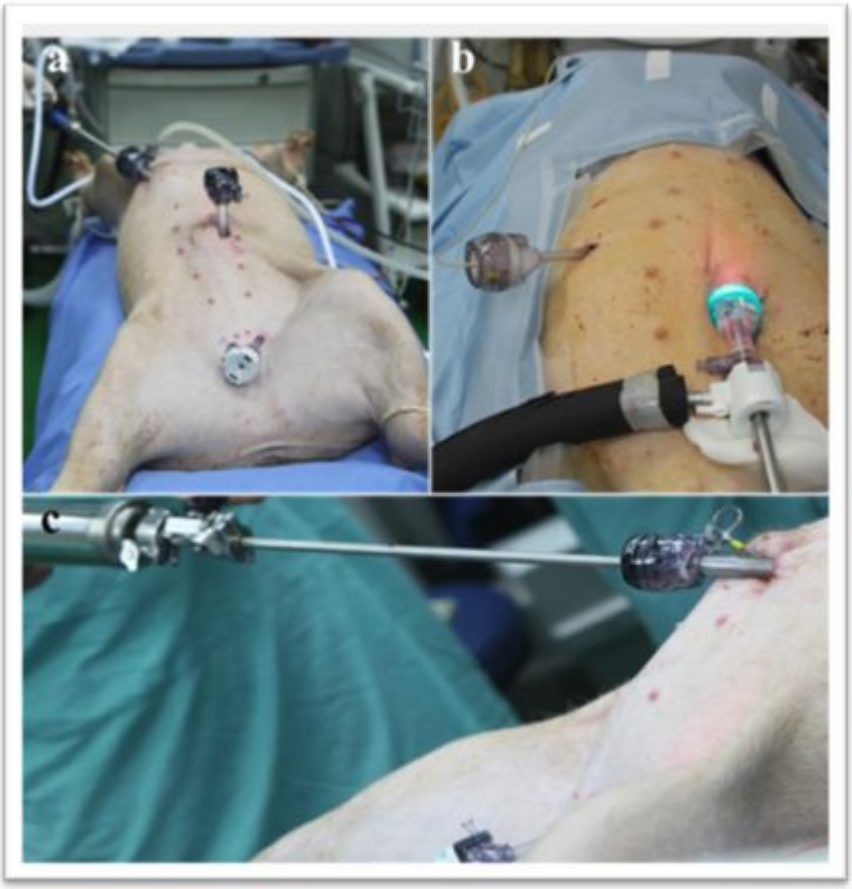
or cisplatin) was 150–250 mL, after reviewing previous studies (11, 12). An esophageal temperature probe for monitoring the intraperitoneal temperature was also inserted through a third 5-mm trocar located at the left lower abdomen. The intraperitoneal pressure was controlled using the Stryker Laparoscopy System. Autopsies were performed immediately at the end of the experiment.

Figure 3.

(a) Three trocars were inserted under pneumoperitoneum of 12 mmHg.

(b) Hyperthermic CO_2 gas was infused through the first, 12-mm trocar located beneath the umbilicus.

(c) A laparoscopic aerosol spray was administered through the first trocar to spray the entire intraperitoneal cavity.



4. Experimental Protocol 2: Survival Model

In the survival model, a pilot experiment (Pig A) was performed to check the experimental protocol, which consisted of the LADG operation, hyperthermic capnoperitoneum, postoperative care for 7 days, and autopsy. After the pilot experiment, the first stage experiment was performed to evaluate the safety of hyperthermic capnoperitoneum. A hyperthermic pressurized intraperitoneal aerosol of indocyanine green (ICG) was administered after insertion of three trocars (Pig B) and LADG (Pig C), without chemotherapeutic agents. After success of the first stage experiment, the second stage experiment was performed to evaluate the safety of H-PAC. In this experiment, H-PAC with cisplatin was administered after insertion of three trocars (Pig D) and LADG (Pig E).

Three trocars were inserted without any operative procedures for two pigs (B and D) to reduce the influence of LADG. Alternatively, LADG for the other three (pigs A, C, and E) was performed in the same manner as for humans (14). The range of the lymph node dissection was D1+, and the type of anastomosis was gastroduodenostomy. The temperature of the intraperitoneal cavity reached 40°C after 30 min infusion of hyperthermic CO_2 gas. One vial of ICG (25 mg) was diluted in 150 mL normal saline (0.9% NaCl), and cisplatin (25 mg, 50 mL) was diluted in 150 mL normal saline

(0.9% NaCl). Diluted ICG (Pigs A–C) or cisplatin (Pigs D and E) was nebulized under hyperthermic capnoperitoneum of 40°C and intra-abdominal pressure of 12 mmHg. Hyperthermic pressurized capnoperitoneum (40°C, 12 mmHg) was maintained for 1 h after infusion. The used ICG or cisplatin aerosol was disposed in a waste water bottle, comprising a closed system (15). Autopsy was performed on postoperative day 7.

III. Results

1. Device Development (Table 1)

Before the porcine model test, many ex vivo tests were performed successfully in the industrial laboratory of WooGun ENG.

We failed to develop the laparoscopic aerosol spray in the first in vivo test because of low CO_2 pressure, but succeeded in the second test after using a thicker CO_2 line that maintained a higher pressure of 40 mmHg. We found that a conventional laparoscopic CO_2 line was suitable.

In addition, the first and second in vivo tests failed because the CO_2 gas was not heated sufficiently. After adding two more heating units to the original two units, the temperature of CO_2 gas was increased to an acceptable level. However, the CO_2 gas lost heat easily during delivery from the device to the porcine model. In the fourth test, covering the CO_2 gas delivery line with a heating line maintained the gas temperature, but the heating line was not cooled immediately. Finally, after a temperature controller was added to the heating line, and in the fifth test, the temperature of the CO_2 gas decreased immediately.

Table 1. Summary of in vivo tests for new device development

Test No.	Date	Spray	Heater		
			Heating	Delivery	Cooling
1	Aug. 8, 2014	F	F		
2	Oct. 17, 2014	S^1	F		
3	Nov. 18, 2014	S	S^2	F	
4	Dec. 12, 2014	S	S	S^3	F
5	Jan. 20, 2015	S	S	S	S^4

F failure, *S* success

S^1: Success after using a thicker CO_2 line that maintained a high pressure of 40mmHg

S^2: Success after adding two more heating units to existing two units

S^3: Success after covering the CO_2 gas delivery line with a heating line

S^4: Success after adding the temperature controller to the heating line

2. Survival Model (Table 2)

In the pilot experiment, the time of anesthesia, LADG, and hyperthermic ICG aerosol infusion was 30, 110, and 90 min, and the pig's intraperitoneal temperature was increased to 38.8–40.2°C. Widespread staining with ICG was observed throughout the intraperitoneal cavity. Following the procedure, the pig was also able drink water, eat food, sleep, and survived for 7 days. Autopsy showed that the surgery wound, anastomosis site, and tissue ultrastructure were all intact.

Including the pilot experiment, the median operation time for LADG was 85 min (80–110 min). Hyperthermic gas was infused for 30 min before administration of the aerosol spray in all five survival model pigs, and aerosol spray time was <5 min. After administration of the aerosol spray, hyperthermic gas was infused for 1 h. The lowest temperature of the intraperitoneal cavity was 38.7°C, and the highest was 41.0°C.

Including the pig in the pilot experiment, all five pigs were given water on postoperative days 1 and 2. They all could drink well from postoperative day 2 onward, and they all received normal feeding from postoperative day 3. Median weight loss was 0.2 kg (0–0.5 kg), and all pigs slept well and survived for 7 days. Autopsies were performed on postoperative day 7. Their wound and anastomosis sites had

completely healed, and no microscopic thermal injury or excessive inflammation was observed in tissues from the stomach, peritoneum, and jejunum.

Table 2. Summary of survival model

Pig	Date	Wt (kg)	Op. (min)	H-PC* (min)	Temperature (°C)	Diet	Wt Change (kg)	Survival (days)	Autopsy		
									Wound	Anastomosis	Tissues§
A (Pilot)	Feb. 9	38.7	110†	90	38.8–40.2	Good	-0.2	7	Intact	Intact	Intact
B	Feb. 16	34.5	10‡	90	38.7–41.0	Good	-0.5	7	Intact	Intact	Intact
C	Feb. 16	34.0	80†	90	38.9–40.8	Good	0	7	Intact	Intact	Intact
D	Feb. 23	36.5	9‡	90	38.8–40.2	Good	0	7	Intact	Intact	Intact
E	Feb. 23	34.5	85†	90	38.8–40.0	Good	-0.5	7	Intact	Intact	Intact

Wt weight, *Op.* operation, *H-PC* hyperthermic pressurized capnoperitoneum

* Hyperthermic gas was infused for 30 min before administration of the aerosol spray. Aerosol spray time was <5 min. After administration of the aerosol spray, hyperthermic gas was infused for 1 h. † Laparoscopy-assisted distal gastrectomy, ‡ Insertion of three trocars, § Tissues of Stomach, peritoneum, and jejunum

IV. Discussion

Peritoneal carcinomatosis is a fatal condition in all types of malignancies. Many patients have already acquired peritoneal carcinomatosis at the time of initial diagnosis or at diagnosis of recurrence after curative-intent surgery and chemotherapy (1, 2). However, there are no standard treatment guidelines for the condition (4). Recently, administration of HIPEC following CRS was shown to increase survival of patients with peritoneal carcinomatosis, and improved types of HIPEC could provide additional benefits (7, 8). Consequently, the purpose of the present study was to develop improved methods of IPC. For this purpose, we developed a device that created hyperthermic capnoperitoneum and maintained a steady temperature for H-PAC, and evaluated the safety of H-PAC in a porcine model.

Before the porcine model test, many ex vivo tests were performed in the industrial laboratory of WooGun ENG. However, we found that the environment of the industrial laboratory differed greatly from that of a hospital operating room or animal laboratory. For example, the electrical power of the industrial laboratory was stronger, and the temperature was higher. As a result, even though the device operated effectively in the lab of WooGun ENG, we needed to modify the device to operate effectively under the weaker hospital electrical power

and lower temperature. Collaboration between engineers and doctors needs more consideration and discussion than the environment does.

During development of the heating apparatus, the heating line that covered the CO_2 gas delivery line was the most important feature. When the CO_2 line was covered by a line that did not create heat, it was impossible to maintain the desired temperature of the gas. Consequently, addition of the heating line increased the temperature of the CO_2 from 37.5 to 40°C. After adopting the heating line, the four heating units caused overheating of the intraperitoneal cavity in the fourth in vivo experiment. From this, we gauged that if the heating line had been incorporated earlier, we would not have required the two additional heating units.

The survival model showed that the heating apparatus created and maintained hyperthermic capnoperitoneum for 90 min at a steady temperature of 39.0–41.0°C. In fact, this apparatus might be expected to maintain hyperthermic capnoperitoneum for >3 h, considering that it was applied to two pigs consecutively on the same experimental day. The survival model also showed that surgical wound, anastomosis, postoperative status, and survival status were not affected significantly by hyperthermic pressurized capnoperitoneum and H-PAC.

IPC has theoretical benefits over systemic chemotherapy in treating peritoneal carcinomatosis: high local concentration of chemotherapeutic

agents and few systemic side effects (5). Combined CRS and HIPEC against peritoneal carcinomatosis of colorectal, gynecological, and gastric origin appear to be superior to other treatment methods (7, 8, 16). Solass et al. developed PIPAC, which might be superior to HIPEC in theory. PIPAC was shown to be superior to HIPEC in terms of distribution and penetration into the peritoneal cavity in an animal model (10). PIPAC showed high local concentration and low systemic exposure using 10% of the usual systemic dose (11, 12). We added the benefits of hyperthermia to the efficacy of PIPAC.

In addition, neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) was effective and well tolerated in patients with advanced gastric cancer and peritoneal carcinomatosis (17). In this NIPS chemotherapy, H-PAC might be the best type of IPC because H-PAC employs the improved distribution and penetration of pressurized aerosol achieved with PIPAC and also the superior antitumor effect of hyperthermia of HIPEC. H-PAC could be used many times easily before or after surgery.

Similar to our effort to improve HIPEC, many surgeons have tried to improve CRS, which has low morbidity and high survival rates (18). For example, Shin et al. reported feasibility of complete mesocolic excision with D3 lymph node dissection in laparoscopic colectomy (19). Kim et al. also presented several cases of laparoscopic

total gastrectomy with D3 lymph node dissection (10th International Gastric Cancer Congress). Minimally invasive CRS has been improved by using better laparoscopic instruments, high-resolution laparoscopes, and well-trained laparoscopic surgeons (20). Therefore, laparoscopic CRS with H-PAC might be a better option than CRS with HIPEC. In addition, HIPEC should only be applied after CRS, while H-PAC can be used during the procedure, which could save 90 min.

This study had several limitations. First, we did not assess improved distribution and penetration of hyperthermic pressurized capnoperitoneum. For such an evaluation, we would have needed to compare the distribution and penetration to that of both PIPAC and HIPEC. This means we should apply HIPEC to additional pigs. We adapted the PIPAC methods of Solass et al., which confirmed the superior distribution and penetration of PIPAC, because we should follow the 3R principles of animal experimentation, especially reduction and because we also observed that staining of the serosal surfaces were well distributed and staining was visible at the back of the peritoneum similar to the results of Solass et al (10).

Second, the efficacy of H-PAC was not evaluated in this experiment because we did not use carcinoma model. Thus, after designing a heating apparatus suitable for human application, H-PAC should be fully evaluated using an appropriate model.

Third, we still need to evaluate the safety of workers providing treatment (15). Compared to other peritoneal chemotherapy treatments, applying H-PAC might result in higher risk of exposure to medical workers. Before applying H-PAC to human patients in the operating room, safety of medical workers providing H-PAC should be evaluated.

Forth, the heating apparatus was made by an engineer for evaluating hyperthermic capnoperitoneum, and it was large and rough. In addition, it was revised many times, which increased its size. It is difficult to adapt such a large piece of equipment to the operating room. This apparatus will need to be redesigned to make it suitable for human application, based on our observations such as a heating line for maintaining the CO_2 gas temperature.

Fifth, we could not apply our results to humans directly. After we revise the machine for sterilization and decide upon the indications for H-PAC and doses of chemotherapeutic agents, we need to receive the approval of the Korean Ministry of Food and Drug Safety for use as a medical device. Solass et al. showed that low-dose doxorubicin has high concentration in the aerosol compared with HIPEC (11). Hence, we should evaluate the dose of chemotherapeutic agents for humans. After making the new heating apparatus suitable for human application, additional animal experiments might be needed for evaluating the feasibility of safety of new heating apparatus, confirming the efficacy

of H-PAC in the carcinoma model, and the deciding the proper dose chemotherapeutic agents.

Steady hyperthermic pressurized capnoperitoneum was created using the heating apparatus developed in this study. H-PAC was evaluated as safe in the porcine survival model. This study is the first step toward applying H-PAC in the treatment of peritoneal carcinomatosis.

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요약(국문초록)

온열 가압 복강내 에어로졸 항암치료의 개발에 대한 돼지 실험

배경: 현재까지도 복막내 파종의 만족스러운 치료법은 없다. 복막내 파종의 치료를 위해 다양한 방법이 시도되고 있다. 그런데 이러한 치료법 중 주목받고 있는 온열 복강내 항암치료는 약물의 복강내 분포와 복막내 종양에의 침투에 한계가 있다. 이러한 한계를 개선한 가압 복강내 에어로졸 항암치료는 온열의 항암 효과 상승이라는 이점을 갖지 못한 단점이 있다. 이에 우리는 온열 복강내 항암치료와 가압 복강내 에어로졸 항암치료의 장점을 합한 '온열 가압 복강내 에어로졸 항암치료'를 위한 기계를 개발하고, 이의 안전성을 돼지 실험을 통해 증명하고자 하였다.

방법: '온열 가압 복강내 에어로졸 항암치료'를 위한 기계는 '복강경 에어로졸 스프레이'와 온열 기복을 만들 수 있는 '히터'로 구성되었다. 우리는 이 기계의 개발을 위해 다섯 마리의 돼지를 실험하였으며, 이 후 다른 다섯 마리의 돼지는 생존 모델로 실험하였다. 최초 생존 모델 실험의 프로토콜 점검을 위해 최초 예비 실험 (돼지 A)이 이루어졌다. 이 후, 3개의 트로카 삽입 후 온열 가압 복강내 인도사이아닌그린 에어로졸 주입 (돼지 B) 및 복강경 보조 위 하부 절제 수술 후 온열 가압 복강내 인도사이아닌그린 에어로졸 주입 (돼지 C)이 항암제 사용 없이 이루어졌다. 다음으로 3개의 트로카 삽입 후 온열 가압 복강내 시스플라틴 에어로졸 항암치료 (돼지 D) 및 복강경 보조 위 하부 절제 수술 후 온열 가압 복강내 시스플라

틴 에어로졸 항암치료 (돼지 E)가 시행되었다. 생존 모델 돼지는 7일간의 생존 후 안락사 및 부검이 이루어졌다.

결과: 수술 평균의 중앙값은 85분 (80-110분) 이었다. 복강 내 온도는 1시간의 온열 가압 복강내 에어로졸 항암치료동안 일정하게 유지되었다 (38.7 - 41.0°C). 다섯 마리 생존 모델 돼지 모두는 건강하게 7일 동안 생존하였다. 체중 감소의 중앙값은 0.2kg였다. 부검을 통해 얻어진 위, 소장, 복막의 조직에서 화상이나 염증으로 인한 이상소견은 관찰되지 않았다.

결론: 온열 가압 복강 내 에어로졸 항암치료는 돼지 실험에서 안전하였다.

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주요어 : 복막내 치료, 항암 치료, 에어로졸, 돼지, 기복, 온열, 복강경 수술

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