Pharmacological effects of carrier fluids on the hyperthermic intraperitoneal chemotherapy using oxaliplatin

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Pharmacological effects of carrier fluids on the hyperthermic intraperitoneal chemotherapy using oxaliplatin

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Background: Carrier fluid plays an important role in the distribution, plasma absorption, chemical stability, and solubility of anticancer agents during hyperthermic intraperitoneal chemotherapy (HIPEC). Because oxaliplatin can be biotransformed in the chloride-containing solutions, it was used to mix chloride-deficient carrier fluids, which can result in postoperative complications. This study aimed to evaluate the pharmacological effects of carrier fluids and to determine the most effective carrier fluid for HIPEC using oxaliplatin from in vitro and in vivo experiments. In addition, we compared the pharmacological properties of oxaliplatin in between hydrophilic and hydrophobic carrier fluids during HIPEC.

Materials and Methods: In vitro study was performed at 25℃, 37℃, and 43℃, respectively, for six carrier fluids, which has different concentrations of chloride ions: normal saline, half saline, 5% dextrose, phosphate buffer saline (PBS), Dianeal® PD-2 peritoneal dialysis solution, and non-chloride Dianeal solution. After mixing 1 ml of 2 mg/ml oxaliplatin into 24 ml of each carrier fluid, the concentration of oxaliplatin was analyzed by high-performance liquid chromatography. The degradation rates of oxaliplatin were measured for 72 hours. An in vivo study was performed using

Sprague-Dawley rats, which divided as subgroups according to the kinds of carrier fluids: 5% dextrose solution, normal saline, half saline, 20% lipid solution, Dianeal® PD-2 1.5% peritoneal dialysis solution, and non-chloride Dianeal® solution. The area under the curve (AUC) of the plasma (AUC_{plasma}), peritoneal fluid AUC (AUC_{fluid}), and peritoneal fluid/plasma AUC ratios were compared in the HIPEC carrier fluids.

Results: In vitro study, the degradation rates of oxaliplatin were significantly different in the carrier fluids according to the time ($p<0.001$). The degradation rates of oxaliplatin were increased in proportion to the concentration of chloride ions in the carrier fluids at 25℃, 37℃ and 43℃, respectively. In addition, the degradation rates of oxaliplatin were acceptable in that they were less than 15% during in vitro study for 30 minutes at 43℃. In the in vivo study, plasma drug concentrations were significantly different in the carrier fluids, varying according to the time. In contrast, the concentration of oxaliplatin in the peritoneal fluid did not change with the carrier fluids. The oxaliplatin AUC ratios of chloride-containing carrier fluids in both normal saline and Dianeal® were higher than those of non-chloride-containing carrier fluids. Although the oxaliplatin AUC_{fluid} did not vary ($p=0.941$), the AUC_{plasma} of the lipid solution was lower than that of the 5% dextrose solution ($p=0.039$).

Conclusion: The most important condition to achieve pharmacological efficacy during HIPEC is to decrease the plasma absorption rates of the anticancer drug. In addition, the chloride-containing isotonic carrier fluids are beneficial in the oxaliplatin-based HIPEC with consideration for pharmacological efficacy as well as for overcoming postoperative adverse events in contrast to hypotonic chloride-deficient carrier fluids.

Key words: intraperitoneal chemotherapy, oxaliplatin, pharmacological, pharmacokinetic, hyperthermic, HIPEC, carrier fluid

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I. INTRODUCTION

Colorectal cancer is the third most common cancer. Approximately 20% of patients with colorectal cancer have metastatic lesion synchronously at the time of diagnosis.[1] In stage IV colorectal cancer, peritoneal carcinomatosis is regarded as having a worse prognosis than visceral metastases to solitary or multiple solid organs.[2,3] Although systemic chemotherapy can infiltrate tumor cores through intravenous routes, it is not sufficient to reach tumor cells, which spread on the peritoneal surface from carcinomatosis. To overcome the poor prognosis of peritoneal carcinomatosis, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) has evolved over three decades.

HIPEC is based on the concept that peritoneal carcinomatosis can be treated with combined loco-regional treatment as well as systemic chemotherapy because anticancer agents can directly contact tumors on the peritoneum through the intraperitoneal route and result in cytotoxic effects. In the treatment of colorectal cancer with peritoneal carcinomatosis, a randomized controlled trial, which was published in 2003, demonstrated that HIPEC after cytoreductive surgery showed

better survival rates in colorectal cancer patients than standard palliative chemotherapy alone.[4] Verwaal et al. reported that the median overall survival rate of the HIPEC group was longer than it was for the palliative chemotherapy group (22.3 months vs. 12.6 months, p=0.032).[4,5]

1. Principal of hyperthermic intraperitoneal chemotherapy

HIPEC after cytoreductive surgery is based on the concepts that microscopic residual tumors can be eradicated by intraperitoneal (IP) administrated anticancer drugs with enhanced cytotoxic effect at 41 to 43℃.[6,7] The primary concept of IP chemotherapy is that tumor tissues are directly exposed to a high concentration of anticancer agents in the peritoneal cavity and absorb them in accordance with the principles of passive diffusion and recirculation into the tumor core through the tumor microcirculation.

Peritoneum is composed of mesothelium, submesothelial tissues, so-called "peritoneal interstitium", and blood capillaries. Dedrick et al. proposed the existence of a peritoneal-plasma barrier, which has a crucial role in sustaining anticancer drugs in the peritoneal interstitium during intraperitoneal chemotherapy.[8-10] The peritoneal-plasma barrier makes it possible to perform IP chemotherapy because it results in slow peritoneal clearance of anticancer agents compared with plasma absorption.[11] Because IP drug administration makes a high concentration gradient in the peritoneal-plasma barriers, anticancer drugs can infiltrate tumors following the principles of convection, diffusion, and recirculation, which are different from systemic chemotherapy, as shown in Figure 1.[6,12,13] Thus, ideal anticancer agents for HIPEC need some factors such as direct penetration into tumor tissues and diffusion of the anticancer agent into inner tumor cores from the re-circulation and antitumor effects.

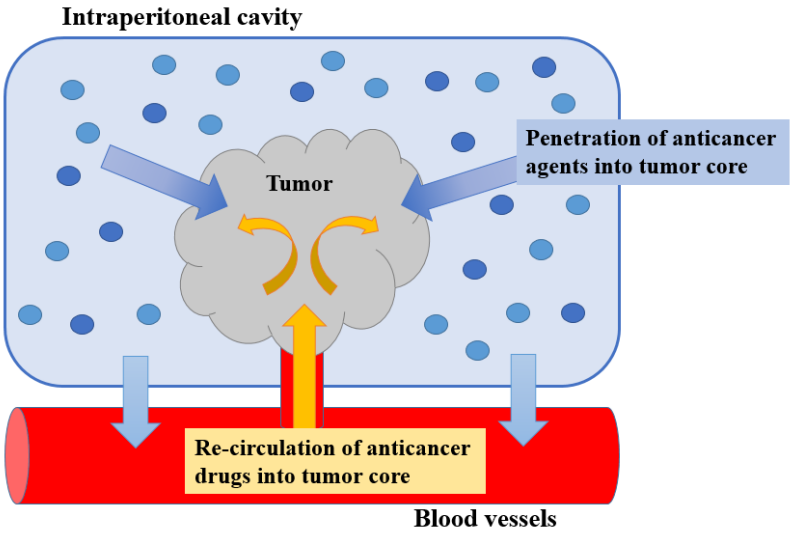


Figure 1. Mechanism of drug absorption during HIPEC

The peritoneal tissue penetration from IP chemotherapeutic agents depends on drug characteristics. Because anticancer drugs have their own chemical properties, they should be considered for their pharmacologic characteristics for use in the peritoneal cavity. In addition, tissue characteristics of peritoneum are also crucial for determining the efficacy of peritoneal penetration of chemotherapeutic agents: permeability of tissue membrane, hydrostatic pressure, and the exposed surface area to the drug.

The fundamental goal of IP chemotherapy is to maximize drug delivery into the peritoneal tumor cells and to minimize systemic circulation, which is related to systemic toxicities of chemotherapeutic agents.[13] Hyperthermia is also beneficial for augmenting cytotoxic effects and increasing the depth of tumor penetration of chemotherapeutic agents.[14] Thus, the ideal condition for HIPEC is a prolonged stay of intraperitoneal drugs, slow clearance of drugs into plasma, and maintained hyperthermia to achieve the increased efficacy of chemotherapeutic agents in the tumor cells of peritoneum.

2. Pharmacologic properties of oxaliplatin

Oxaliplatin is a third generation platinum compound with a diamino-cyclohexane and oxalate ligand (Figure 2). It is an alkylating agent with cytotoxic action by causing inter- and intrastrand cross-links with DNA.

Because oxaliplatin prevents tumor progression through DNA adduction in the tumor cells, it is commonly used to treat gastrointestinal tract malignancies. In the treatment of colon cancer, oxaliplatin using 5-flourouracil (5-FU) and leucovorin is regarded as first-line treatment for systemic chemotherapy.

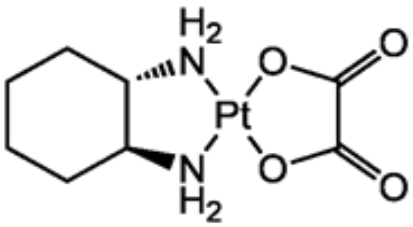


Figure 2. Molecular structure of oxaliplatin

3. Instability of oxaliplatin in chloride-containing fluids

Although oxaliplatin is still regarded as a promising drug for colorectal cancer, its rapid clearance rate and short half-life time of 15 minutes are regarded as its disadvantages in terms of its use for IP chemotherapy.[5,6] Therefore, HIPEC using oxaliplatin is performed for 30 minutes with bidirectional chemotherapy with 5-FU.[15,16]

Oxaliplatin can be biotransformed by water and nucleophiles such as Cl^- and HCO_3^- (Figure 3). The degradation of oxaliplatin in aqueous media tends to depend on the concentration of chloride-ions as well as the pH.[17] In addition, native oxaliplatin is known with a low level of cytotoxicity. The biotransformation products

of oxaliplatin such as the dichloro-platinum compound Pt(dach)Cl_2 have stronger cytotoxic effects than native compounds.[18] Thus, because the oxalate ligand of oxaliplatin can be easily substituted by chloride-containing solutions, oxaliplatin-based HIPEC clinically used a dextrose solution as a carrier solution to maintain the molecular stability of oxaliplatin such as the rate of drug absorption, plasma clearance rate, and cytotoxicity.[6,7,13]

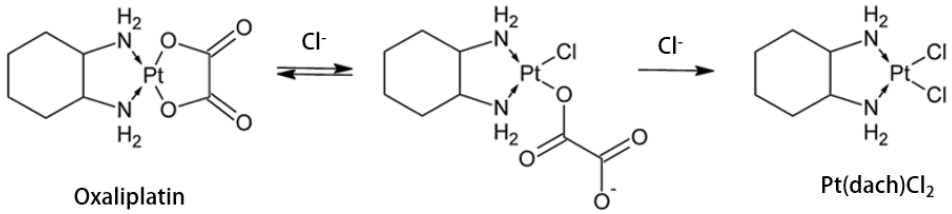


Figure 3. Transformation of oxaliplatin in chloride-containing fluids

However, the hypotonicity of the dextrose carrier solution resulted in severe electrolyte imbalance, hyperglycemia, tissue edema, and intraperitoneal hemorrhagic complications after HIPEC.[11,19-21] To overcome the intrinsic drawbacks of oxaliplatin as the platinum compound, there were some efforts to improve the efficacy of oxaliplatin during HIPEC in the aspects of drug modification and its carrier solutions. Mehta et al. suggested using oxaliplatin in chloride-containing carrier solutions during HIPEC because the degradation of oxaliplatin was about 10% of the small amount in the chloride-containing HIPEC carrier solution.[18,22] In addition, the drug delivery system of anticancer drugs had been developed to prolong the efficacy in the peritoneal cavity such as liposomes or micelles.[23] Because lipid layers can decrease the water solubility of anticancer agents, it makes it possible to decrease clearance rates and to increase the absorption rate in the peritoneum.[24]

4. The purpose of this study

Tissue penetration of anticancer agents during HIPEC depends on several pharmacologic properties during HIPEC including drug concentration, time of exposure, molecular weight, temperature and liphophilicity.[25] To satisfy optimal HIPEC treatments, appropriate matching between the anticancer drug and its carrier solution are crucial to enhancing drug activities during HIPEC because their pharmacologic properties are uniquely different in terms of their use in the peritoneal cavity. In particular, carrier solutions have important roles in terms of contributing drug distribution, plasma clearance, structural stability and solubility of anticancer agents during HIPEC. In this study, we aimed to investigate pharmacologic characteristics of oxaliplatin according to the kinds of HIPEC carrier solutions in order to find optimal pharmacologic conditions to treat colorectal cancer patients. In addition, we evaluated whether the lipophilic properties of the carrier solution can improve the absorption rate of anticancer drugs during oxaliplatin-based HIPEC compared with hydrophilic carrier solutions.

II. MATERIALS AND METHODS

1. In vitro stability test of oxaliplatin in carrier fluids

A. Experimental design

An in vitro study was performed at 25℃, 37℃, and 43℃, respectively. The temperature 25℃ represents a room temperature, 37℃ a body temperature, and 43℃ the condition of HIPEC. The six kinds of carrier fluids, which have different concentrations of chloride ions were used in vitro: normal saline, half saline, 5% dextrose, phosphate buffer saline (PBS), Dianeal® PD-2 peritoneal dialysis solution, and non-chloride Dianeal solution. The 1 ml of 2 mg/ml oxaliplatin was mixed with 24 ml of each carrier fluid. The concentration of oxaliplatin was analyzed at 0 (starting point), 15, 30, 45, 60, 90, 120 min, 4hr, 6hr, 12hr, 24hr, 48hr, and 72hr using high-performance liquid chromatography (HPLC). The experiments that were repeated three times were performed for all carrier fluids at the conditions of the following temperatures: 25℃, 37℃, and 43℃.

B. Analytic method

The oxaliplatin concentration in the carrier fluids was measured by the HPLC system (1200 Infinity series, Agilent technology, Santa Clara, USA). The HPLC system was composed of a pump (1260 Quat Pump VL), a column heater (1260 TCC), an auto sampler (1260 ALS), and a UV detector (1260 VWD VL). The column that was used was XTerra™ RP18, 4.6×250 mm, particle size 5 ㎛ (Waters Corporation, USA). The mobile phase was performed with 20% of ACN and 80% of DW. The run time was 4 minutes and used UV 210 nm and 20μL of injection volume. The flow rate was 1 ml/min and the temperature of the column was sustained at 30℃.

C. Statistical method

Statistical analyses were performed using SAS (Statistical Analysis Software version 9.3; SAS Institute Inc., Cary, NC, USA). The comparison of drug concentrations between carrier fluids according to time was analyzed by a linear mixed model. The mean profile plot was used to compare the concentration graphs of oxaliplatin in the carrier fluids according to the time. A p-value less than 0.05 was regarded as statistically significant.

2. In vivo study: pharmacological properties of oxaliplatin according to carrier fluids

An in vivo study was designed to evaluate two main subjects. One subject is to evaluate pharmacological properties of oxaliplatin in the HIPEC carrier fluids, which contains different concentrations of chloride-ions. The other subject is to compare the pharmacologic properties of oxaliplatin between hydrophilic and hydrophobic carrier fluids during HIPEC. The main experimental settings and analytic methods for in vivo studies are demonstrated below.

A. Experimental design

Six kinds of carrier fluids were evaluated for in vivo study: 5% dextrose solution, 0.9% normal saline, 0.45% half saline, 20% lipid solution (Lipision®, JW Pharmaceutical, Republic of Korea), Dianeal® PD-2 1.5% peritoneal dialysis solution (Baxter, USA), and non-chloride Dianeal solution, which is composed of Dianeal® PD-2 peritoneal dialysis solution without chloride ions. Three rats per group were used in this study. The Animal Research Committee of Yonsei University (IACUC Number A-201708-311-01) and Ajou University (IACUC Number 2016-0029), Republic of Korea approved the study protocols. Experiments for in vivo study

according to carrier fluids were performed at Yonsei University College of Pharmacy, Incheon, Republic of Korea from July to December 2017. Experiments to compare hydrophilic and hydrophobic carrier fluid during oxaliplatin-HIPEC were performed at the Laboratory Animal Research Center at Ajou University Medical Center, Suwon, Republic of Korea from April to October 2016.

B. Components of carrier fluids for HIPEC

The chloride concentration of 0.9% normal saline is 154 mEq/L, whereas 0.45% half saline is 77 mEq/L and Dianeal® PD-2 peritoneal fluid solution is 96 mEq/L. Both 5% dextrose solution and non-Cl^- Dianeal solution are not contained with chloride ions. Lipision® is fat emulsion, which is composed of purified soybean oil, purified phospholipid, and glycerin. The detailed components of carrier fluid are demonstrated in Table 1.

Table 1. The components of hydrophilic carrier fluids

	Normal saline	Half saline	5% dextrose	Dianeal®	Non-Cl^- Dianeal
Na (mEq/L)	154	77	0	132	132
Cl (mEq/L)	154	77	0	96	0
Osmolarity (mOsm/L)	308	154	272	346	346
Tonicity	Isotonic	Hypotonic	Isotonic	Hypertonic	Hypertonic

C. Animals

The 8-week-old male Sprague-Dawley rats, weighing 290g to 320 g, were purchased from Orientbio Inc. (Kyunggi-do, Republic of Korea). The mean body surface area (BSA) was 0.03 to 0.04 m^2, which was calculated using the Du Bois

method (BSA=0.007184 × height$^{0.725}$ × weight$^{0.425}$).[13] Rats were housed in filter-top cages for 1 week before the experiments with free access to food and water (Ziegler® lab animal diet, USA). The animal laboratory was kept under standard conditions with a temperature of 21-24℃, humidity of 40-60%, 12-hour light cycle, and filtered air.

D. Experimental settings for HIPEC

The HIPEC experimental equipment was set up as shown in Figure 4. The HIPEC chamber, which we made by ourselves using acryl-plates, had three lines: inflow, outflow, and suction-connection lines. The inflow line was inserted into the roller of a peristaltic pump (Masterflex C/L pump®, Barnant, USA) and delivered HIPEC solutions at a flow rate of 40 ml/min. The outflow line connected the abdominal cavity to a reservoir chamber. Outflow line circulating fluids could be returned to the reservoir chamber by using negative pressure induced by suction. The temperature of circulating HIPEC solutions was maintained at 41-42℃. Both inflow and outflow lines were heated by a circulating warm bath (Lauda E100®, Lauda, Germany). Three sites were monitored for a consistent temperature using thermometers: circulating HIPEC solutions in the rat abdominal cavity and rectum, and the heated water in the warm bath.

E. Hyperthermic intraperitoneal chemotherapy (HIPEC) procedure

All animals received general inhalation anesthesia using 3% isoflurane with 1:1 oxygen and nitrous oxide before HIPEC procedures. Before the anesthesia, 20 ml of water was given orally to all rats to prevent dehydration. In accordance with the coliseum technique,[14] a 4-5 cm medial longitudinal incision was made in the rat's abdominal wall. Then, all margins of the abdominal wall were elevated and fixed in the acryl plates, which were located 15 cm above the basal plate. After setting the

HIPEC equipment as described in Figure 4, HIPEC solutions were prepared with 460 mg/m^2 of oxaliplatin, which were mixed with 300 ml of carrier fluid. HIPEC was performed over 60 minutes. Blood and peritoneal fluid samples were collected until 60 minutes after beginning HIPEC. Peritoneal fluid was collected in the HIPEC-circulated fluid of the abdominal cavity, and blood samples were collected from the retro-orbital venous sinus after inhalation anesthesia. All samples were kept frozen at -60°C until further analyses were undertaken.

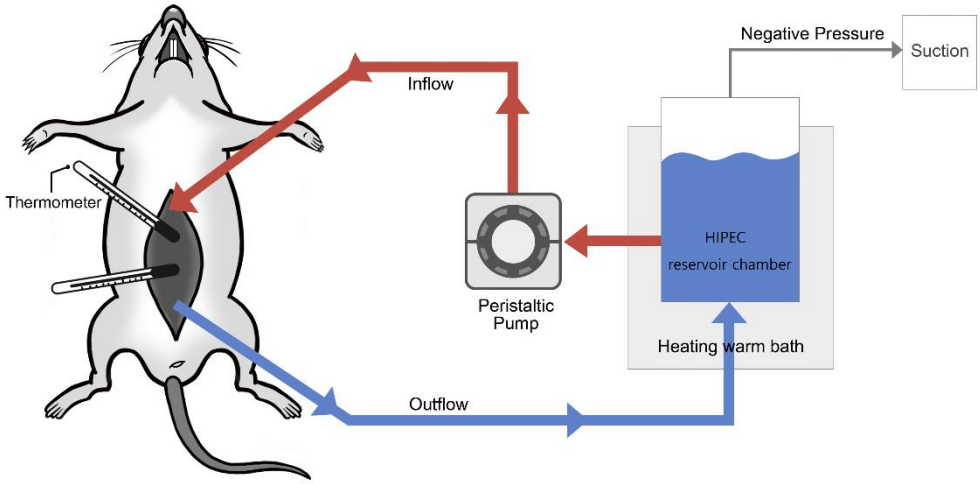


Figure 4. The HIPEC rat model

F. Sample preparation and analytical methods

Samples were thawed at room temperature before analysis of drug concentration was undertaken. Protein precipitation was performed in all samples to remove blood and peritoneal components, which can interfere with analytical results.

Oxaliplatin was analyzed by inductively coupled plasma-quadrupole mass spectrometry (ICP-QMS; NexION 300D®, PerkinElmer, USA). Because ICP-QMS measures the platinum concentration of oxaliplatin, it has advantages to measure the

precise concentration of oxaliplatin. To measure the platinum complex in the oxaliplatin, samples were prepared using a microwave digestion system. Samples were placed in Teflon vessels with 5 ml of HNO3 and digested in a microwave oven at 800 W for 1 hour. After diluting to 25 ml with distilled water, samples were analyzed by ICP-QMS. All samples were analyzed at Advanced Analysis Center of Korea Institute of Science and Technology.

G. Statistical analyses

Statistical analyses were performed using SPSS (Statistical Product and Service Solution 23 for Windows; SPSS Inc., Chicago, IL, USA), SAS (Statistical Analysis Software version 9.3; SAS Institute Inc., Cary, NC, USA), and R 3.4.1 software (The R Foundation for Statistical Computing). Linear mixed models were used to compare drug concentrations between carrier fluids according to time. The one-way analysis of variance (ANOVA) was used to compare the area under the curve (AUC) ratios among carrier fluids. Post-hoc analyses were performed using the Bonferroni and Scheffe correction method. The estimated formulas for the graphs were calculated by using the random intercept model and the estimated slopes were compared with the linear mixed model. A p-value less than 0.05 was considered to be statistically significant.

III. RESULTS

1. In vitro stability test for the oxaliplatin

A. The degradation rate of oxaliplatin according to the carrier fluids

(A) The temperature condition of 25℃

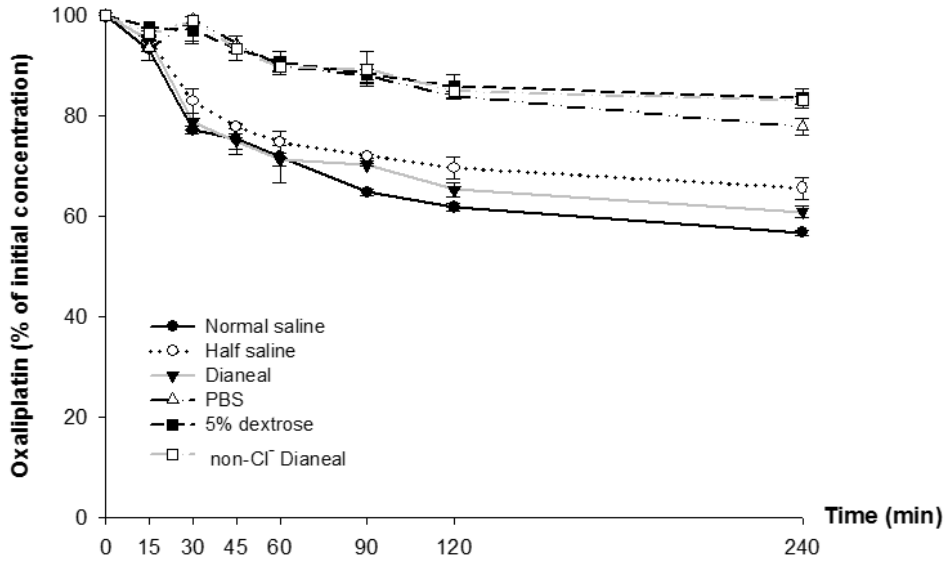
The degradation rates of oxaliplatin were significantly different in the carrier fluids according to the time ($p<0.001$). In addition, the degradation rates of oxaliplatin were dependent on the concentration of chloride ions in the carrier fluids. As demonstrated in Figure 5, both 5% dextrose solution and non-Cl^- Dianeal solution, which are not contained chloride-ions, showed a lower rate of degradation of oxaliplatin than chloride-containing carrier fluids. The concentration of oxaliplatin in 5% dextrose solution was 97.1% and non-Cl^- Dianeal was 98.9%, whereas normal saline was 77.1% in 30 minutes. In addition, the differences of the degradation rate between chloride-containing and non-chloride-containing carrier fluids were increased at 72 hours. Oxaliplatin remained at 72 hours in 69.7% of 5% dextrose solution, 72.8% of non-Cl^- Dianeal, 10.8% of normal saline, 23.3% of half saline, and 14.5% of Dineal®. Normal saline, which contains the highest chloride ion in the carrier fluids, showed the highest degradation rate at 72 hours. Thus, the degradation rates of oxaliplatin increased in proportion to the concentration of chloride ions in the carrier fluids at 25℃ (Table 2).

Table 2. Comparison of oxaliplatin degradation rates at 25℃

	Normal saline	Half saline	Dianeal®	PBS	5% dextrose	Non-Cl^- Dianeal	Overall p-value
Temp 25℃							
0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	Group: <0.0001
15min	93.2±0.4	95.1±1.2	95.1±0.2	93.4±2.4	97.6±0.1	96.3±0.7	Time : <0.0001
30min	77.1±0.8	83.0±2.4	78.8±1.7	99.2±1.3	97.1±2.8	98.9±3.9	Group*time: <.0001
45min	75.4±3.1	77.9±0.5	74.9±1.6	94.4±1.4	93.5±2.5	93.4±0.9	
60min	71.8±5.2	74.7±0.6	71.2±1.3	90.0±1.1	90.7±2.3	89.7±0.9	
90min	64.8±0.6	72.0±0.4	70.2±0.3	88.0±1.2	88.4±2.0	89.4±3.5	
2hr	61.8±0.8	69.6±2.1	65.3±1.4	83.9±0.6	85.8±2.3	84.9±0.1	
4hr	56.8±0.5	65.6±2.2	60.8±1.2	77.8±1.7	83.5±2.0	83.0±0.8	
6hr	53.0±0.4	60.3±1.1	57.8±1.2	73.6±4.1	80.9±2.2	80.9±0.9	
12hr	44.9±0.3	55.8±0.2	56.6±6.4	70.6±1.3	78.3±2.1	77.5±0.6	
1day	34.0±2.6	48.0±2.4	40.4±0.4	60.8±4.7	75.2±2.0	78.1±0.7	
2days	16.8±0.5	38.1±4.3	26.7±2.7	37.8±0.5	71.9±1.8	77.4±3.5	
3days	10.8±5.7	23.3±0.7	14.5±0.6	24.5±2.4	69.7±2.0	72.8±1.4	

PBS, phosphate buffer saline.

A



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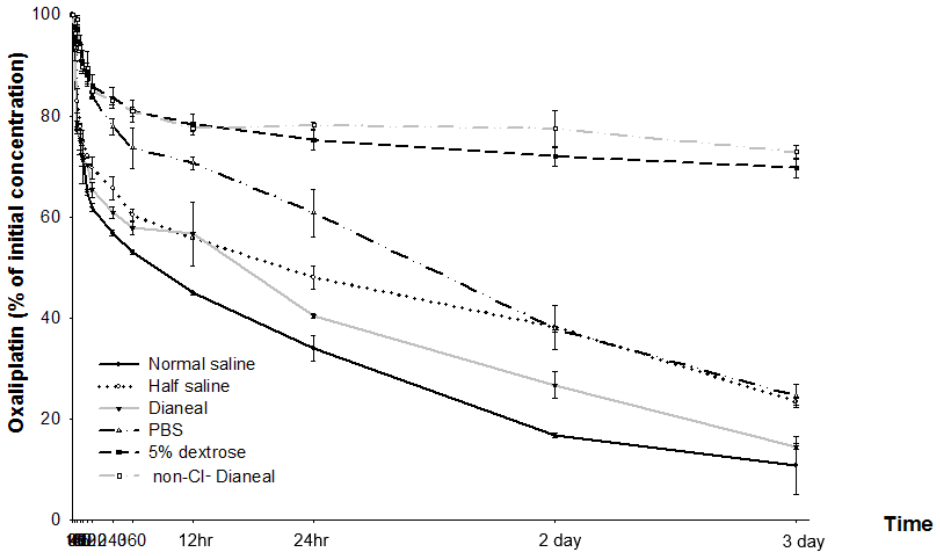


Figure 5. The oxaliplatin concentration at 25℃ (A-Degradation rate within 240 min; B-Degradation rate until 72hr).

(B) The temperature condition of 37℃

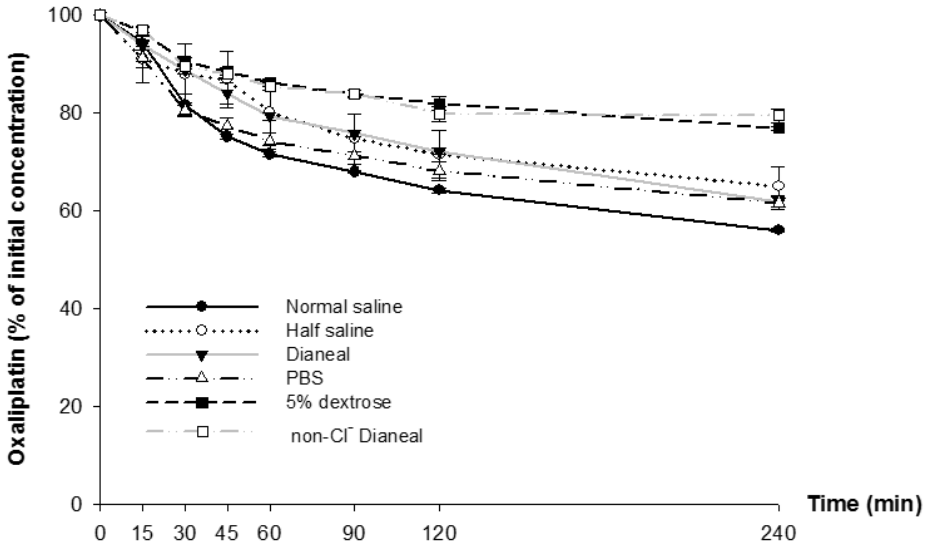
The degradation rates of oxaliplatin at a temperature of 37℃ were different in the carrier fluids according to the time ($p<0.001$). The concentrations of oxaliplatin in non-chloride-containing carrier fluids such as 5% dextrose and non-Cl^- Dianeal were about 10% higher than in chloride-containing carrier fluids after 30 minutes: 90.6% of 5% dextrose vs. 81.7% of normal saline. 49.3% of oxaliplatin remained in the normal saline, whereas 75.1% of oxaliplatin remained in the 5% dextrose solution after 6 hours (Figure 6A). Although oxaliplatin remained from 0% to 4.3% in the chloride-containing carrier fluids, it remained between 63.3% and 71.3% in the non-chloride-containing carrier fluids after 72 hours. As demonstrated in Figure 6B, the difference between the degradation rates of oxaliplatin in the carrier fluids was an increase between chloride- and non-chloride-containing carrier fluids. In addition, the degradation rates of oxaliplatin were proportional to the concentration of chloride ions in the carrier fluids at a temperature of 37℃ (Table 3).

Table 3. Comparison of oxaliplatin degradation rates at 37℃

	Normal saline	Half saline	Dianeal®	PBS	5% dextrose	Non-Cl^- Dianeal	Overall p-value
Temp 37℃							
0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	Group: <0.0001
15min	94.3±0.6	91.0±5.0	93.9±0.9	91.1±1.8	96.8±1.1	97.0±0.6	Time : <0.0001
30min	81.7±2.3	88.0±6.0	88.8±1.0	80.4±1.2	90.6±0.9	89.5±0.6	Group*time: <.0001
45min	75.1±0.5	86.8±5.8	84.0±2.3	77.4±1.6	88.5±0.8	88.1±0.9	
60min	71.5±0.5	80.2±6.7	79.3±0.9	74.2±1.8	86.2±0.8	85.5±0.8	
90min	67.9±0.3	74.7±5.2	75.9±0.7	71.3±0.8	83.8±0.8	83.9±0.6	
2hr	64.2±0.6	71.5±4.9	72.2±0.7	68.1±2.0	81.9±1.5	79.8±1.6	
4hr	56.0±0.4	65.0±4.1	61.9±1.2	61.6±1.2	76.9±0.5	79.4±1.4	
6hr	49.3±0.4	60.4±4.1	55.8±1.2	56.3±1.4	75.1±1.0	76.4±0.7	
12hr	35.9±0.3	50.4±3.5	43.3±1.2	46.9±0.6	71.7±0.8	76.3±0.7	
1day	17.1±0.0	33.2±1.9	25.7±0.8	33.6±6.8	68.2±0.9	74.7±0.6	
2days	2.3±0.2	14.5±1.1	10.9±0.2	17.2±6.5	66.2±0.8	72.6±0.5	
3days	0.0±0.0	4.3±0.5	4.3±0.2	2.9±1.9	63.3±0.6	71.3±0.4	

PBS, phosphate buffer saline.

A



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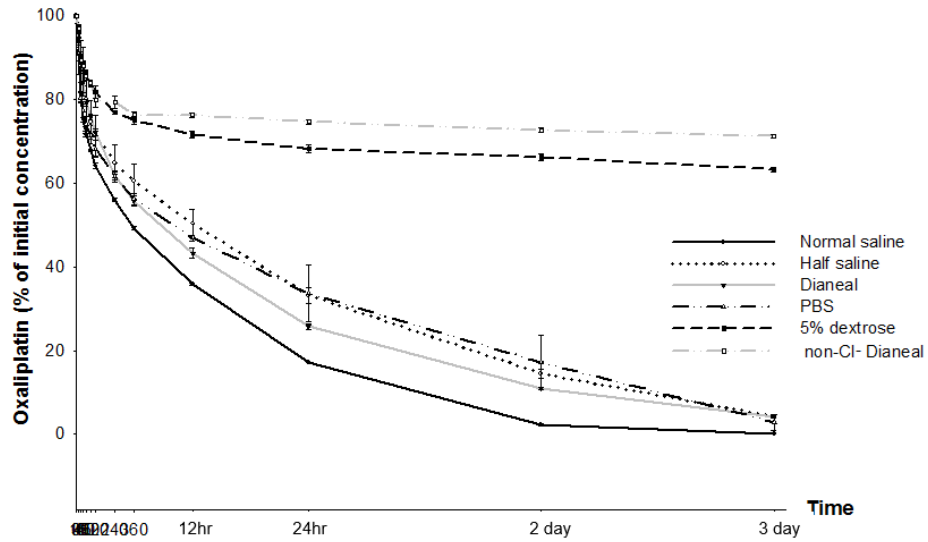


Figure 6. The oxaliplatin concentration at 37℃ (A-Degradation rate within 240 min; B-Degradation rate until 72hr).

(C) The degradation rates of oxaliplatin at 43℃

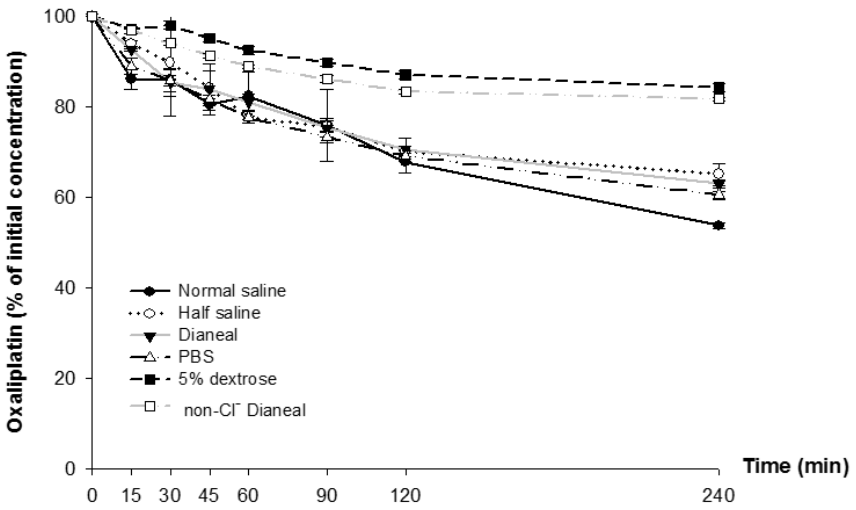
The degradation rates of oxaliplatin at a temperature of 43℃ were significantly different in the carrier fluids according to the time ($p<0.001$). The concentration of oxaliplatin in 5% dextrose solution was 98.0%, which was higher than the 86.0% of normal saline at 30 minutes. Although the oxaliplatin concentration was reduced in the chloride-containing media by half after about 6 hours, it remained at more than 80% of oxaliplatin in the non-chloride-containing carrier fluids (Table 4). 70.3% of oxaliplatin remained in the 5% dextrose solution at 3 days, whereas oxaliplatin did not remain in either normal saline or Dianeal®. The differences of the remaining oxaliplatin concentration between chloride-containing and non-chloride-containing carrier fluids were significantly increased until 72 hours. In addition, the degradation rates of oxaliplatin were increased in proportion to the concentration of chloride ions in the carrier fluids, as demonstrated in Figure 7.

Table 4. Comparison of oxaliplatin degradation rates at 43℃

	Normal saline	Half saline	Dianeal®	PBS	5% dextrose	Non-Cl^- Dianeal	Overall p-value
Temp 43℃							
0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	Group: <0.0001
15min	86.2±2.4	94.1±0.7	92.6±0.3	89.0±1.8	97.3±0.1	97.0±0.7	Time: <0.0001
30min	86.0±2.6	89.7±11.8	85.4±3.0	85.8±1.2	98.0±0.9	94.0±0.5	Group*time: <.0001
45min	80.5±1.2	84.1±3.8	84.0±5.6	81.7±0.9	95.2±0.9	91.3±0.6	
60min	82.5±5.3	77.6±0.4	81.1±1.8	77.7±1.3	92.5±0.9	88.9±0.4	
90min	76.0±7.9	75.7±1.4	75.3±2.1	73.3±1.2	89.8±0.7	86.2±0.8	
2hr	67.8±2.4	70.2±1.1	70.5±2.7	69.1±0.6	87.1±0.8	83.4±0.6	
4hr	53.7±0.7	65.1±2.5	63.0±0.8	60.5±0.9	84.3±0.8	81.8±0.4	
6hr	44.2±0.2	64.3±2.3	54.4±2.0	50.8±1.3	81.4±0.7	80.5±1.0	
12hr	27.0±0.4	47.1±4.7	36.0±0.7	30.8±1.6	78.3±0.7	78.7±0.7	
1day	8.7±0.0	22.0±0.6	21.5±0.7	12.4±0.1	74.6±0.7	75.3±0.1	
2days	0.5±0.0	10.5±4.5	8.8±2.6	2.6±0.6	72.8±0.7	64.4±1.2	
3days	0.0±0.0	5.1±3.9	0.0±0.0	2.0±1.1	70.3±0.6	58.5±2.8	

PBS, phosphate buffer saline.

A



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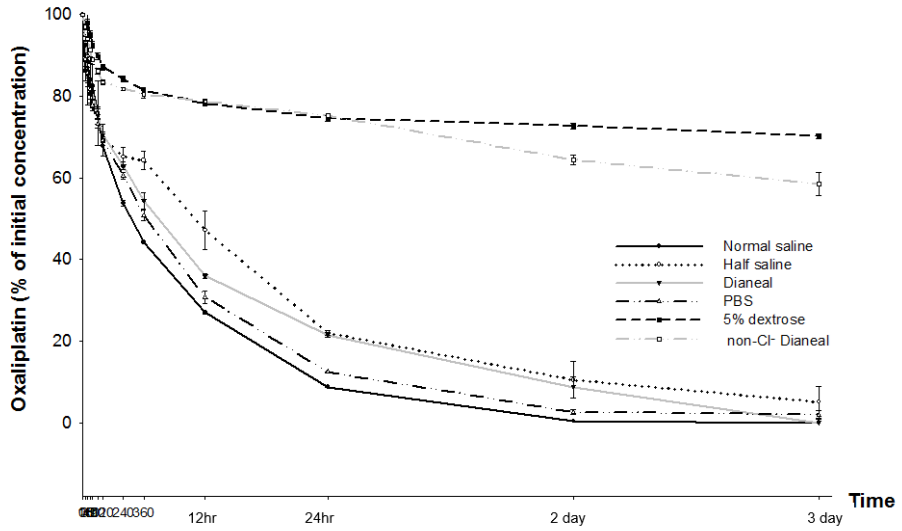

Figure 7. The oxaliplatin concentration at 43℃ (A-Degradation rate within 240 min; B-Degradation rate until 72hr).

B. Comparison for the degradation of oxaliplatin in the carrier fluids according to the temperature (25℃ vs. 37℃ vs. 43℃)

According to the temperature, the degradation rates of oxaliplatin were significantly different in all carrier fluids ($p<0.001$) (Table 5). However, there was no statistical significance for the concentration of oxaliplatin in all carrier fluids within 30 minutes at 25℃, 37℃, and 43℃, respectively. In 30 minutes, the concentration of oxaliplatin in 5% dextrose solution was 98.0% and in non-Cl^- Dianeal it was 94.0% at 43℃. As shown in Figure 8, there was no significant difference among the three conditions of temperature. During 72 hours, the degradation rates of oxaliplatin at a temperature of 43℃ were higher than at 25℃ and 37℃ in carrier fluids, except for 5% dextrose (Figure 9). However, the 5% dextrose solution showed similar degradation rates in all temperature conditions (25℃ vs. 37℃, $p=0.6673$; 25℃ vs. 43℃, $p=0.9743$; 37℃ vs. 43℃, $p=0.6440$). While oxaliplatin in the chloride-containing carrier fluid was almost completely degraded after 72 hours, it remained at 70.3% in 5% dextrose and 58.5% in non-Cl^- Dianeal at a temperature of 43℃.

Table 5. The concentration of oxaliplatin in the carrier fluids according to the temperature (25℃ vs. 37℃ vs. 43℃)

	Normal saline (%)			Half saline (%)			Dianeal® (%)			PBS (%)			5% dextrose (%)			Non-Cl⁻Dianeal (%)		
	25℃	37℃	43℃	25℃	37℃	43℃	25℃	37℃	43℃	25℃	37℃	43℃	25℃	37℃	43℃	25℃	37℃	43℃
0 min	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
15 min	93.2	94.3	86.2	95.1	91.0	94.1	95.1	93.9	92.6	93.4	91.1	89.0	97.6	96.8	97.3	96.3	97.0	97.0
30 min	77.1	81.7	86.0	83.0	88.0	89.7	78.8	88.8	85.4	99.2	80.4	85.8	97.1	90.6	98.0	98.9	89.5	94.0
45 min	75.4	75.1	80.5	77.9	86.8	84.1	74.9	84.0	84.0	94.4	77.4	81.7	93.5	88.5	95.2	93.4	88.1	91.3
60 min	71.8	71.5	82.5	74.7	80.2	77.6	71.2	79.3	81.1	90.0	74.2	77.7	90.7	86.2	92.5	89.7	85.5	88.9
90 min	64.8	67.9	76.0	72.0	74.7	75.7	70.2	75.9	75.3	88.0	71.3	73.3	88.4	83.8	89.8	89.4	83.9	86.2
120 min	61.8	64.2	67.8	69.6	71.5	70.2	65.3	72.2	70.5	83.9	68.1	69.1	85.8	81.9	87.1	84.9	79.8	83.4
4hr	56.8	56.0	53.7	65.6	65.0	65.1	60.8	61.9	63.0	77.8	61.6	60.5	83.5	76.9	84.3	83.0	79.4	81.8
6hr	53.0	49.3	44.2	60.3	60.4	64.3	57.8	55.8	54.4	73.6	56.3	50.8	80.9	75.1	81.4	80.9	76.4	80.5
12hr	44.9	35.9	27.0	55.8	50.4	47.1	56.6	43.3	36.0	70.6	46.9	30.8	78.3	71.7	78.3	77.5	76.3	78.7
1day	34.0	17.1	8.7	48.0	33.2	22.0	40.4	25.7	21.5	60.8	33.6	12.4	75.2	68.2	74.6	78.1	74.7	75.3
2day	16.8	2.3	0.5	38.1	14.5	10.5	26.7	10.9	8.8	37.8	17.2	2.6	71.9	66.2	72.8	77.4	72.6	64.4
3day	10.8	0.0	0.0	23.3	4.3	5.1	14.5	4.3	0.0	24.5	2.9	2.0	69.7	63.3	70.3	72.8	71.3	58.5

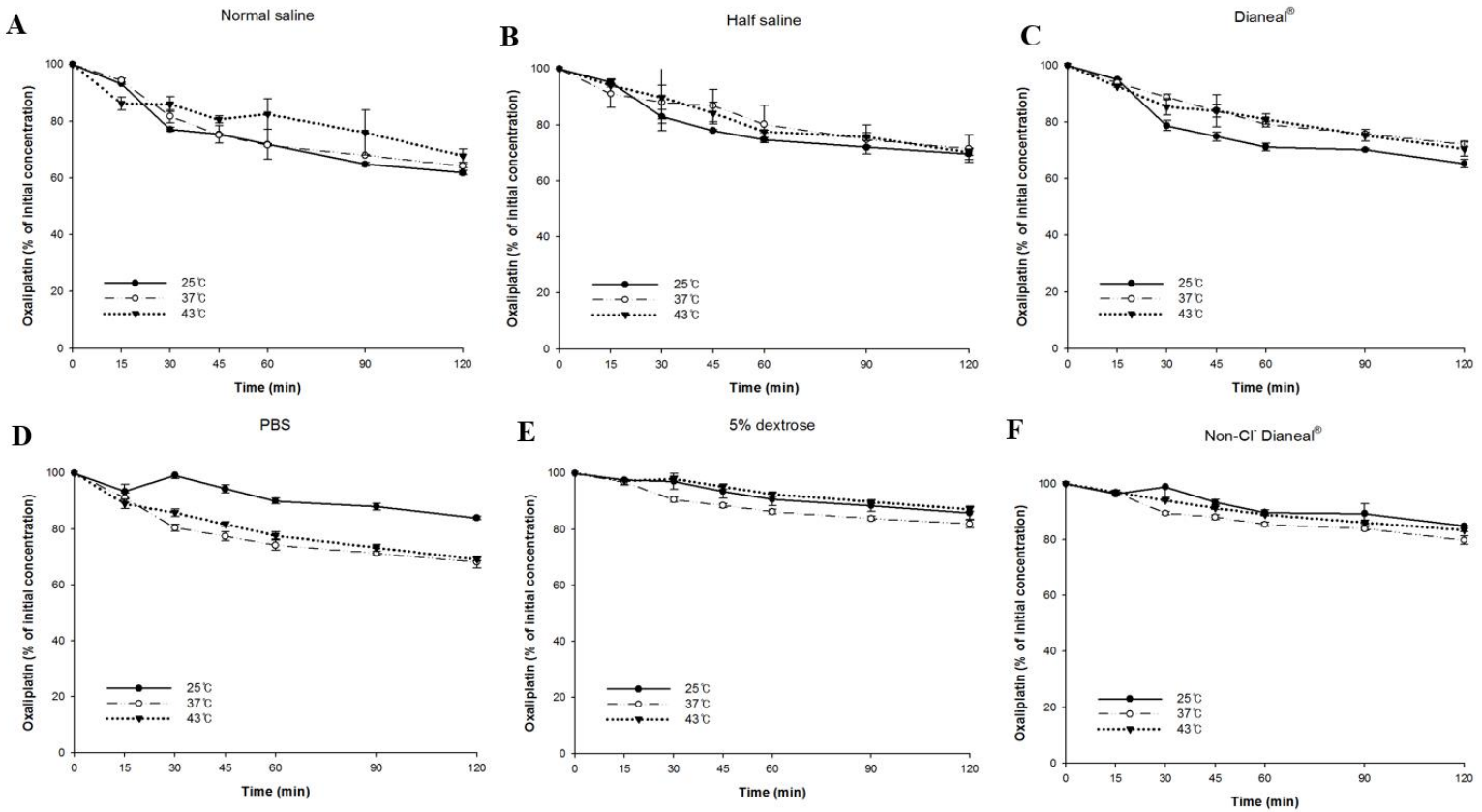

Figure 8. Degradation rate of oxaliplatin during 120 min at 25℃, 37℃, and 43℃ (A-Normal saline; B-Half saline; C-Dianeal®; D=PBS; E-5% dextrose; F-Non-Cl^- Dianeal)

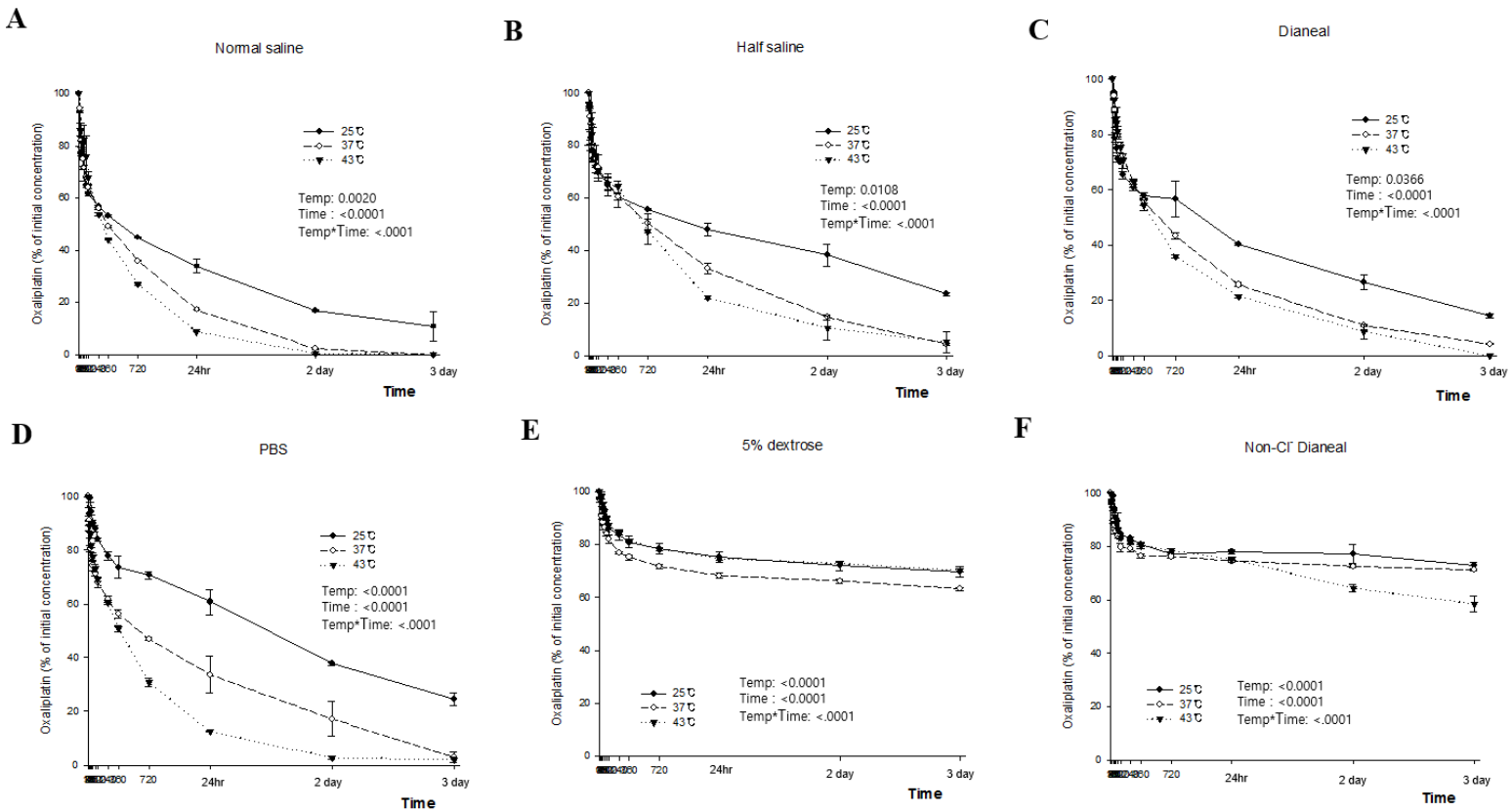

Figure 9. Degradation rate of oxaliplatin until 3 days at 25°C, 37°C, and 43°C (A-Normal saline; B-Half saline; C-Dianeal®; D=PBS; E-5% dextrose; F-Non-Cl^- Dianeal)

2. In vivo study for the stability of oxaliplatin according to the carrier fluids

A. Drug concentrations of oxaliplatin in the peritoneal fluid

The concentrations of oxaliplatin were not significantly different in the carrier fluids according to the time (p=0.3013). As shown in Figure 10, there was no statistical difference of oxaliplatin concentration during HIPEC of 60 minutes in all carrier fluids.

Table 6. The time-dependent drug concentration of oxaliplatin in the peritoneal fluid

Samples	Time (min)	Drug concentration of oxaliplatin in the carrier fluid (ng/mL)					
		Normal saline	Half saline	5% Dextrose	Non-Cl^- Dianeal	Dianeal®	Overall p-value†
Peritoneal fluid	0	34125.0 ±625.0	33000.0 ±1561.2	35666.7 ±2670.2	33250.0 ±2912.8	34041.7 ±72.2	Group: 0.1928 Time: 0.0385 Group* Time: 0.3013
	10	33291.7 ±904.3	30208.3 ±3241.2	34062.5 ±4036.5	29916.7 ±4081.8	31937.5 ±1084.3	
	20	34250.0 ±1111.0	28000.0 ±2689.7	29458.3 ±2867.7	29625.0 ±5291.5	30125.0 ±1984.3	
	30	33333.3 ±1812.9	30250.0 ±3520.0	37083.3 ±6119.0	26708.3 ±12003.5	33125.0 ±1317.0	
	40	32875.0 ±1317.0	30458.3 ±3424.0	33916.7 ±3996.7	28916.7 ±7376.4	33875.0 ±3526.7	
	50	34458.3 ±2306.0	28833.3 ±3246.0	32166.7 ±6452.1	27666.7 ±7182.2	28375.0 ±3616.4	
	60	32666.7 ±616.6	26005.0 ±5.0	33958.3 ±8450.5	31666.7 ±2812.7	27208.3 ±4430.6	

Mean±Standard deviation. †The linear mixed model was used to calculate p values.

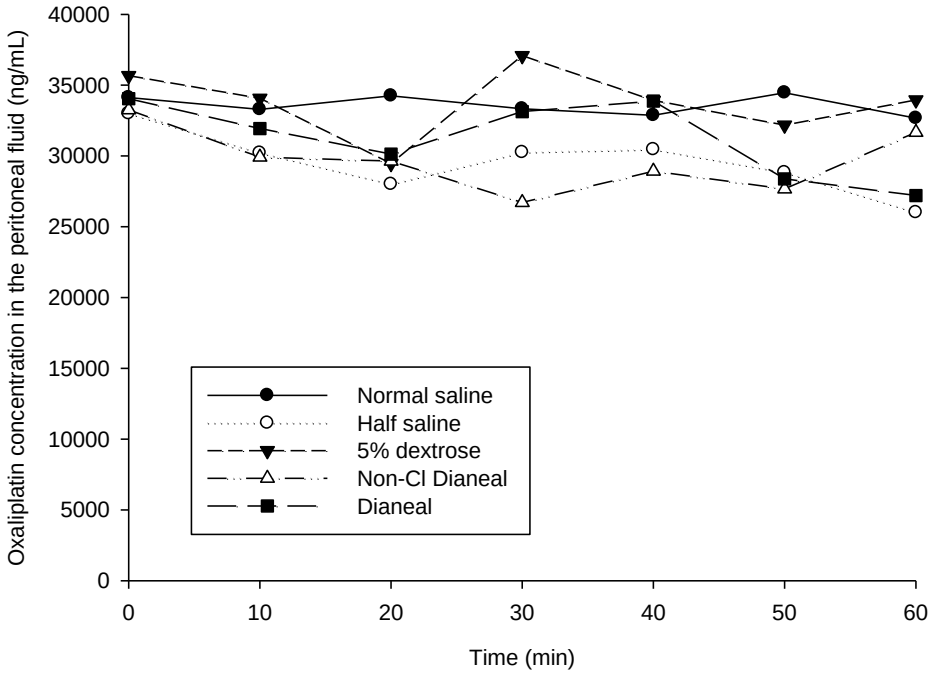

Figure 10. The concentration of oxaliplatin in the plasma by carrier fluids

B. Drug concentrations of oxaliplatin in the plasma

The plasma drug concentrations of oxaliplatin were significantly different among the carrier fluids by time (p=0.0321). The plasma absorption rates of oxaliplatin were sequentially increased according to time. However, the concentration of oxaliplatin was highest in the half saline. The plasma concentration of oxaliplatin in both 5% dextrose and non-Cl- Dianeal showed higher rates than in Dianeal® or normal saline (Figure 11).

Table 7. The time-dependent drug concentration of oxaliplatin in the plasma

Samples	Time (min)	Drug concentration of oxaliplatin in the carrier fluid (ng/mL)					
		Normal saline	Half saline	5% Dextrose	Non-Cl⁻ Dianeal	Dianeal ®	Overall p-value
Plasma	0	0.0±0.0	0.0±0.0	0.0±0.0	0.000 ±0.000	0.0±0.0	Group: 0.0014 Time: <0.0001 **Group*Time: 0.0321**
	10	502.1 ±122.1	556.3 ±364.0	894.2 ±228.7	792.1 ±128.6	472.9 ±149.0	
	20	885.8 ±183.0	1950.4 ±1241.3	1508.3 ±182.1	1640.4 ±418.4	761.7 ±304.1	
	30	1271.3 ±343.5	2904.2 ±1904.0	2625.0 ±673.3	2408.3 ±456.9	1383.3 ±268.8	
	40	1658.3 ±568.2	4941.7 ±1133.3	3650.0 ±1256.3	3325.0 ±632.3	1837.5 ±612.5	
	50	2162.5 ±659.0	5480.000 ±1341.203	4079.167 ±830.694	4045.833 ±682.520	2329.167 ±415.770	
	60	2650.0 ±595.3	5630.0 ±5.0	3829.2 ±906.3	4820.8 ±901.8	3241.7 ±761.6	

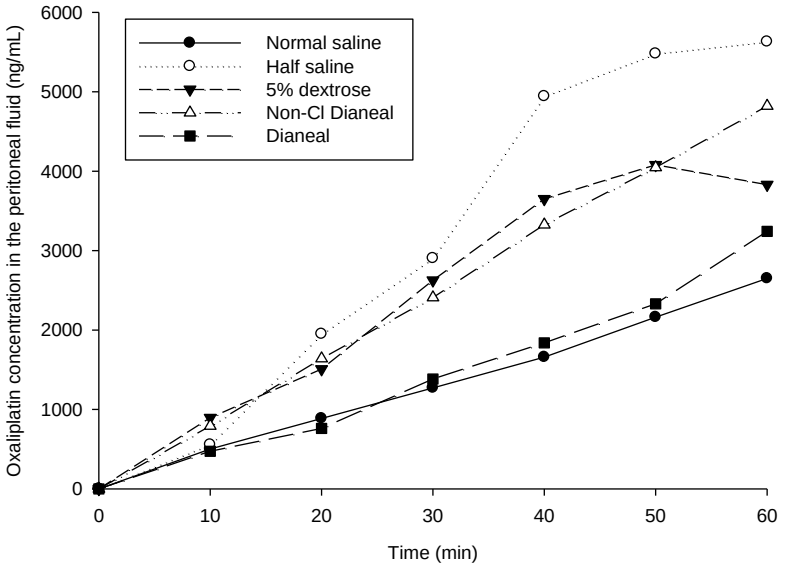

Figure 11. The concentrations of oxaliplatin in the peritoneal fluid by carrier fluids

C. Comparison of AUC ratios in the carrier fluids during HIPEC

The comparison for AUC_{fluid} was not significantly different in all carrier fluids (p=0.3907). However, AUC_{plasma} were different in the carrier fluids (p=0.0037). In particular, non-chloride-containing carrier fluids such as 5% dextrose and non-Cl^- Dianeal showed a higher rate of AUC_{plasma} than chloride-containing carrier fluid except half saline. On the other hand, oxaliplatin AUC ratios of chloride-containing carrier fluid, which are both normal saline and Dianeal®, were higher than non-chloride-containing carrier fluids. According to the post-hoc analysis in Table 9, there was no significant difference of AUC ratios between normal saline and Dianeal®. However, the AUC ratio of normal saline was two times higher than 5% dextrose solution after 60 minutes of HIPEC (27.0 vs. 13.9, p=0.0102). Half saline showed the highest AUC_{plasma} and the lowest AUC ratio out of all the carrier fluids.

According to the AUC ratios of oxaliplatin, which were cut off at 30 minutes, the AUC ratios for all carrier fluids were higher than those at 60 minutes (Table 10). Although there were no significant differences in AUC_{fluid} among carrier fluids, the AUC_{plasma} of chloride-containing carrier fluids such as normal saline or Dianeal® was lower than chloride-deficient carrier fluids. The AUC ratio of normal saline was 52.1, which was the highest value in all the carrier fluids.

Table 8. The AUC ratios in the carrier fluids

Area under the curve (AUC)	Carrier fluids					
	Normal saline	**Half saline**	**5% Dextrose**	**Non-Cl^- Dianeal**	**Dianeal®**	**Overall p value**
AUC_{fluid}	2016042 ±51970.3	1772525 ±154881.8	2015000 ±174992.2	1752917 ±382504.3	1880625 ±82053.7	0.3907
AUC_{plasma}	78050.00 ±19859.3	186475.0 ±53228.2	146712.5 ±15465.1	146220.8 ±22817.7	84054.2 ±5249.9	**0.0037**
AUC ratio	**27.0** ± 6.8	**9.9** ± 2.0	**13.9** ±2.7	**11.9** ± 0.9	**22.4** ±1.6	**0.0005**

Mean±Standard deviation; AUC ratio=AUC_{fluid} /AUC_{plasma}

Table 9. Post-hoc analysis for AUC ratios for carrier fluids

	AUC_{fluid}	AUC_{plasma}	AUC ratio
NS vs. Half saline	**>0.9999**	**0.0086**	**0.0013**
NS vs. 5DW	**>0.9999**	**0.141**	**0.0102**
NS vs. Non-Cl^- Dianeal	>0.9999	0.1463	0.0036
NS vs. Dianeal®	**>0.9999**	**>0.9999**	**>0.9999**
Half saline vs. 5DW	>0.9999	>0.9999	>0.9999
Half saline vs. Non-Cl^- Dianeal	>0.9999	>0.9999	>0.9999
Half saline vs. Dianeal®	>0.9999	0.0128	0.0132
5DW vs. Non-Cl^- Dianeal	>0.9999	>0.9999	>0.9999
5DW vs. Dianeal®	>0.9999	0.22	0.1371
Non-Cl^- Dianeal vs. Dianeal®	>0.9999	0.2282	0.0416

NS, normal saline; 5DW, 5% dextrose; the Bonferroni method was used for post-hoc analysis.

Table 10. The AUC ratios in the carrier fluids during 30 minutes of HIPEC

Area under the curve (AUC)	Carrier fluids					
	Normal saline	Half saline	5% Dextrose	Non-Cl^- Dianeal	Dianeal®	Overall p value
AUC_{fluid}	1012708± 12660.43	898333.3± 81644.1	998958.3± 61546.9	895208.3± 166684.5	956458.3± 36621.7	0.3907
AUC_{plasma}	20235.4± 4718.8	39587.5± 21887.5	37150.0± 7333.2	36366.7± 7259.0	19262.5± 4483.5	**0.0037**
AUC ratio	52.1±13.5	27.0±12.6	27.7±6.0	24.7±0.5	51.4±11.0	**0.0005**

Mean±Standard deviation; AUC ratio=AUC_{fluid} /AUC_{plasma}

D. Estimated formula of drug concentration in the plasma

The plasma concentration gradient of anticancer drugs was calculated using a linear mixed model according to time to estimate the changes in plasma drug concentration among the carrier fluids. As shown in Table 11, the estimated plasma

concentration gradient of oxaliplatin was significantly different according to the kinds of carrier fluids ($p<0.0001$). The estimated concentration gradient of oxaliplatin in half saline was 99.148, which was steeper than it was for both normal saline ($p=0.0018$) and Dianeal® ($p=0.0065$). However, there was no significant difference for the estimated plasma concentration gradient between Dianeal® and normal saline.

Table 11. Estimated formula of oxaliplatin in the plasma

	Carrier fluids	Estimated formula of the graph	Estimated concentration gradient (SE)	Overall P-value
Plasma	**Normal saline**	19.602+43.607*time	43.607(6.796)	**<0.0001**
	Half saline	-53.127+99.148*time	99.148(6.796)	
	5% dextrose	73.682+73.335*time	73.335(6.796)	
	Non-Cl⁻ Dianeal	-0.939+80.685*time	80.685(6.796)	
	Dianeal®	-11.736+52.303*time	52.303(6.796)	

Table 12. Post-hoc analysis for estimated plasma concentration gradients

	P-value
NS vs. Half saline	**0.0018**
NS vs. 5DW	0.1139
NS vs. Non-Cl⁻ Dianeal	0.0317
NS vs. Dianeal®	**>0.9999**
Half saline vs. 5DW	0.2287
Half saline vs. Non-Cl⁻ Dianeal	0.8369
Half saline vs. Dianeal®	0.0065
5DW vs. Non-Cl⁻ Dianeal	**>0.9999**
5DW vs. Dianeal®	0.5349
Non-Cl⁻ Dianeal vs. Dianeal®	0.1446

NS, normal saline; 5DW, 5% dextrose; the Bonferroni method was used for post-hoc analysis.

3. In vivo study for the comparison of pharmacologic effects of oxaliplatin between hydrophilic and hydrophobic carrier fluids

A. Comparison of drug concentrations over time during HIPEC

The plasma drug concentrations were significantly different among the carrier fluids by time (p=0.0049) (Table 13 and Figure 12). The plasma concentration of oxaliplatin was increased during 60 minutes. The plasma absorption rate was highest in the oxaliplatin mixed with 5% dextrose solution group. However, oxaliplatin concentrations in the peritoneal fluid were not significantly different among the carrier fluids (p=0.6249), as shown in Table 14 and Figure 13.

Table 13. The concentration of anticancer drugs between hydrophilic and hydrophobic carrier fluids in the plasma during HIPEC

Time (min)	Dianeal®	5% Dextrose solution	Lipid solution	Overall p value†
0	0.0±0.0	0.0±0.0	0.0±0.0	
5	331.3±3.8	633.2±121.6	276.2±52.0	
10	433.2±121.0	892.4±447.7	440.4±112.0	Carrier fluid p=0.0048
20	928.5±240.1	2548.6±1406.8	906.7±363.5	Time: p<0.0001
30	1503.9±555.1	3045.5±397.9	1129.6±428.9	**Carrier fluid* Time: p=0.0049**
45	2356.9±1238.4	4627.5±1346.4	2126.0±1403.9	
60	3667.1±1527.2	7093.9±946.1	2541.9±966.1	

Mean±Standard deviation; †The linear mixed model was used to calculate p values and to compare the concentration of anticancer drugs among carrier fluids according to the time.

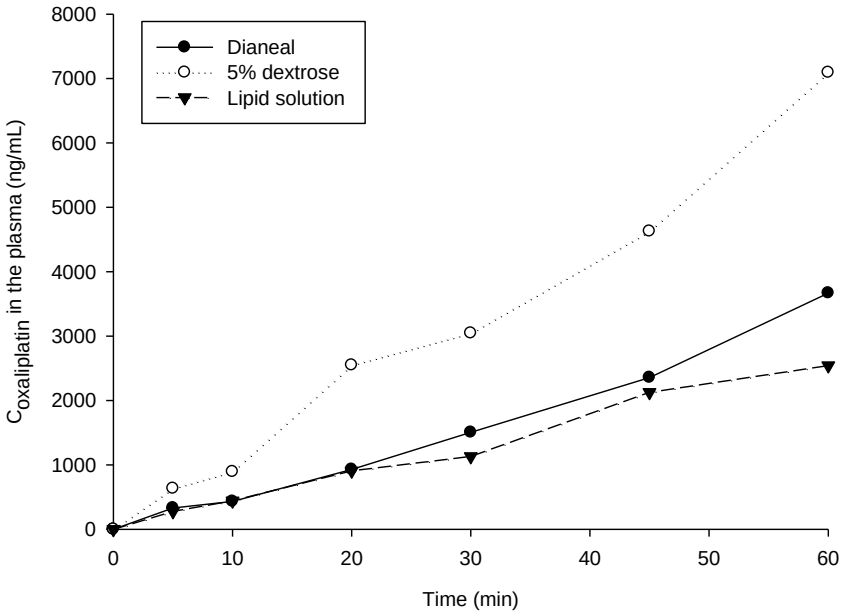

Figure 12. The concentrations of oxaliplatin in the plasma according to carrier fluids

Table 14. The concentration of anticancer drugs in the peritoneal fluid between hydrophilic and hydrophobic carrier fluids during HIPEC

Time (min)	Dianeal®	5% Dextrose solution	Lipid solution	Overall p value†
0	34053.1±1020.0	34172.5±2721.1	24162.1±6562.2	
5	29652.3±2882.0	33323.1±6834.2	23444.7±6613.9	
10	27671.9±2273.3	32907.0±3919.8	25220.9±6078.8	Carrier fluid: p=0.0307
20	30573.2±5042.3	29145.2±2315.7	25870.7±6310.5	Time: p=0.7322
30	28737.9±5267.0	31320.5±5696.8	29700.3±7873.8	**Carrier fluid* Time: p=0.6249**
45	30996.5±2960.2	32412.8±2838.9	26504.4±7815.0	
60	27329.7±4951.2	30239.3±598.2	26755.2±8213.6	

Mean±Standard deviation; †The linear mixed model was used to calculate p values and to compare the concentration of anticancer drugs among carrier fluids according to the time.

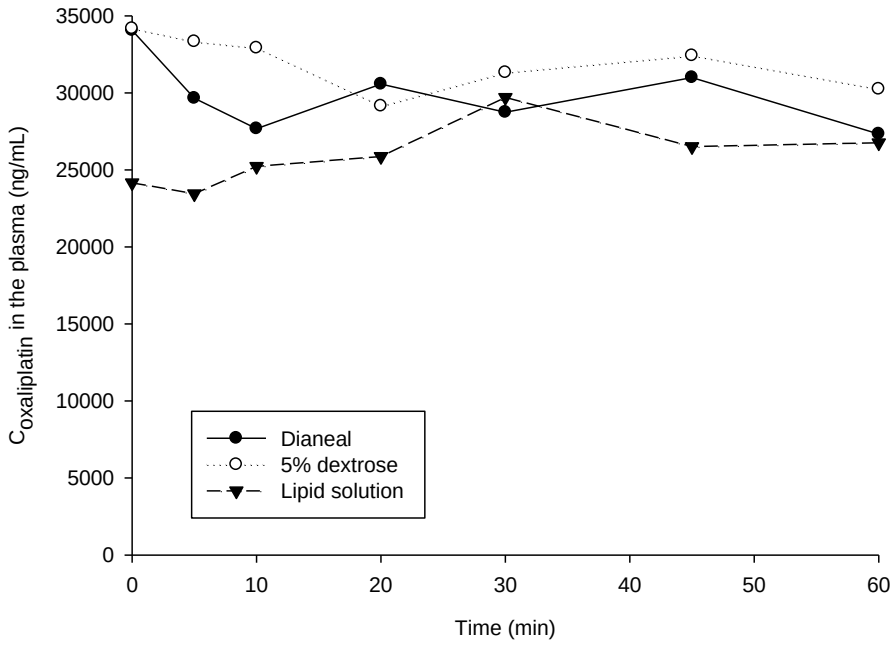

Figure 13. The concentrations of oxaliplatin in the peritoneal fluid according to carrier fluids

B. Comparison of AUC ratios between water and lipid solutions

The AUC_{fluid} was not significantly different among the carrier fluids (p=0.941). However, the AUC_{plasma} of the 5% dextrose solution was higher than that of the lipid solution (p=0.039). There was no significant difference in the AUC_{plasma} between the 5% dextrose solution and Dianeal® (p=0.070). The oxaliplatin AUC ratio was different among the carrier fluids. In particular, the oxaliplatin AUC ratio in the lipid solution was marginally higher than that of the 5% dextrose solution during HIPEC (p=0.056) (Table 15).

According to the AUC ratios of oxaliplatin, which were cut off at 30 minutes, the AUC ratios for all the carrier fluids were higher than those at 60 minutes: the AUC ratio of Dianeal®= 38.3, 5% dextrose=20.2, and lipid solution= 42.0. Although there were no significant differences in AUC_{fluid} among carrier fluids, the AUC_{plasma} of 5%

dextrose solution was significantly different compared to the Dianeal® or lipid solution (p=0.032). Both the AUC_{plasma} and the AUC ratio of the lipid solution were higher than those of the 5% dextrose solution (Table 16).

Table 15. Comparison of AUC ratios between hydrophilic and hydrophobic carrier fluids during 60 minutes of HIPEC

Carrier fluids	Dianeal®	5% Dextrose solution (5DW)	Lipid solution	P value††	Post-hoc analysis§		
					P value (Dianeal vs. 5DW)	P value (Dianeal vs. Lipid)	P value (5DW vs. Lipid)
AUC_{fluid}	1671286± 176313.1	1690563± 411394.1	1594976± 418625.8	0.941	0.998	0.966	0.947
AUC_{plasma}	95540.1±3 9851.3	196029.4 ±47823.8	78824.3± 37743.6	**0.028**	0.070	0.890	**0.039**
AUC ratio*	19.3±6.6	8.7±1.6	22.2±6.1	**0.046**	0.125	0.806	**0.056**

AUC ratio*= AUC_{fluid}/AUC_{plasma}; ††One-way analysis of variances among groups (ANOVA); §Post-hoc analysis was calculated by the Scheffe correction method.

Table 16. Comparison of AUC ratios of oxaliplatin during 30 minutes of HIPEC

Carrier fluids	Dianeal®	5% Dextrose solution (5DW)	Lipid solution	P value† †	Post-hoc analysis§		
					P value (Dianeal vs. 5DW)	P value (Dianeal vs. Lipid)	P value (5DW vs. Lipid)
AUC_{fluid}	775502.7± 137773	904413.1± 160077.2	776209.1± 192779.2	0.576	0.653	>0.9999	0.656
AUC_{plasma}	21092.3±5 986.7	49536.9± 18242.4	18945.4± 6092.5	**0.032**	0.064	0.975	**0.049**
AUC ratio*	38.3±10.2	20.2±8.2	42.0±5.6	**0.040**	0.102	0.850	**0.051**

AUC ratio*= AUC_{fluid}/AUC_{plasma}; ††One-way analysis of variances among groups (ANOVA); §Post-hoc analysis was calculated by the Scheffe correction method.

C. Plasma drug concentration gradient by carrier fluids

The estimated plasma concentration gradient of oxaliplatin had a steeper slope in the 5% dextrose solution compared to both the Dianeal® and the lipid solution ($p<0.001$). However, there was no significant difference in the oxaliplatin estimated plasma concentration gradient between the Dianeal® and lipid solutions ($p=0.3957$).

Table 17. Estimated formulas for the anticancer drug concentration in the plasma

Carrier fluids	Estimated formulas of the graph for the plasma drug concentrations	Estimated concentration gradient (SE)	P-value†
Dianeal®	C_{plasma} = 59.15•time – 126.21	59.15 (7.52)	**<0.0001** (Dianeal vs. 5DW, p<0.001; Dianeal vs. Lipid, p=0.3957 5DW vs. Lipid, p<0.001)
5% Dextrose solution	C_{plasma} = 113.21•time – 57.74	113.21 (7.35)	
Lipid solution	C_{plasma} = 43.05•time + 14.56	43.05 (7.35)	

C_{plasma}, Concentration of plasma; SE, Standard error; 5DW, 5% Dextrose; p-value †, calculated by linear mixed model; Estimated formulas were calculated by the random intercept model.

IV. DISCUSSION

HIPEC after cytoreductive surgery is regarded as suitable for treating peritoneal carcinomatosis because a high intensified drug concentration can penetrate tumor tissues and infiltrate tumor cores through the peritoneal-plasma barrier.[10] In addition, hyperthermia and cytotoxicity of anticancer agents can augment drug penetration into remnant cancer cells in the peritoneum. To satisfy the oncologic benefits after HIPEC, it is crucial to determine proper anticancer agents and their carrier fluids because each drug has its own characteristics which are of use for intraperitoneal chemotherapy. In HIPEC treatment of colorectal cancer patients with peritoneal carcinomatosis, mitomycin-C or oxaliplatin are widely used drugs. Mitomycin-C is an antitumoral antibiotic. It has advantages for use in intraperitoneal chemotherapy because it is a hydrophilic anticancer drug with a longer half-life than oxaliplatin. However, mitomycin-C has antitumoral effects depending on the activation of cytochrome P450 reductase and its enzyme activity in the tumors.[26] On the other hand, oxaliplatin is a platinum-based alkylating agent, which is a promising anticancer agent for treating metastatic colorectal cancer by employing 5-fluorouracil- (5-FU) based regimens such as FOLFOX chemotherapy. Although mitomycin-C-based HIPEC uses isotonic carrier fluids or Dianeal® peritoneal dialysis solution, the optimal selection of the carrier solution during oxaliplatin HIPEC is still debated.

Oxaliplatin is the third-generation platinum compound, which has antineoplastic activity through the formation of DNA adducts.[27,28] The 1,2-diaminocyclohexane (dach)-platinum adducts are bulkier and more effective in inhibiting DNA synthesis than cisplatin-adducts.[21,29] The oxalate ligand can be substituted into chloride ions and reacts with biotransformation products such as $Pt(dach)Cl_2$, which is more cytotoxic than oxaliplatin.[30,31] Thus, the instability of oxaliplatin, which is degraded in a chloride-containing carrier solution resulted in using non-chloride-containing carrier fluids during HIPEC. Until now, 5% glucose solution has been regarded as the proper carrier solution in HIPEC using oxaliplatin.[20] Elias et al. reported favorable

oncological outcomes from using oxaliplatin with 5% dextrose carrier solution in bidirectional HIPEC treatment.[14] However, it has been reported that the hypotonicity of the dextrose solution increases the risk of postoperative complications after HIPEC, such as severe electrolyte imbalance, hyperglycemia, tissue edema, and intraperitoneal hemorrhagic complications.[9,17-19] To overcome these drawbacks of carrier fluid in oxaliplatin-based HIPEC, it is required to find alternative carrier fluids and to understand pharmacologic properties for oxaliplatin-based HIPEC. Therefore, in this study, we evaluated the degradation of oxaliplatin according to the chloride-containing solutions in vitro at the temperature condition of 25℃, 37℃, and 43℃. The degradation rates of oxaliplatin were evaluated depending on the chloride concentration of HIPEC carrier fluids during HIPEC in vivo. Then, the comparative study between hytrophilic and hydrophilic carrier fluids during oxaliplain-HIPEC was evaluated.

In the in vitro study, the chloride concentration of the carrier fluids was related to the degradation rates of oxaliplatin at all the temperature conditions: 25℃, 37℃, and 43℃. The non-chloride-containing carrier fluids such as 5% dextrose solution and non-Cl^- Dianeal remained more than 90% until 30 minutes. The degradation rates of oxaliplatin in the non-chloride-containing carrier fluids were lower than in chloride-containing carrier fluids. In addition, the degradation rates of oxaliplatin were proportional to the concentration of chloride ions in the carrier fluids. Mehta et al. reported that the degradation rate of oxaliplatin was less than 10% after 30 minutes and oxaliplatin degradation was related to the biotransformation of $Pt(dach)Cl_2$.[22] Oxaliplatin is activated in vivo from the biotransformation into active forms such as Pt(dach)Cl(OH) or $Pt(dach)Cl_2$. However, $Pt(dach)Cl_2$ is more slowly converted than Pt(dach)Cl(OH).[28] Therefore, oxaliplatin in the carrier fluids is mostly inactive because of its low rate of degradation and slow conversion.[17]

In comparison with oxaliplatin concentration according to the temperature, degradation rates of oxaliplatin were not statistically significant in all carrier fluids within 30 minutes. However, oxaliplatin remained in higher rates at 25℃ than 37℃

or 43℃ in all carrier fluids. As the temperature was increased, the degradation rates of oxaliplatin were increased during three days. However, the concentration of oxaliplatin in all the carrier fluids was not significantly different at 30 minutes. Because oxaliplatin is clinically used for HIPEC during 30 minutes, we think that HIPEC at the temperature condition of 43℃ is acceptable.

In the in vivo study, the oxaliplatin concentrations in the peritoneal fluid were not significantly different in all the carrier fluids: normal saline, half saline, 5% dextrose, Dianeal® PD-2 solution, and non-Cl^- Dianeal solution. On the other hand, the plasma absorption rates of oxaliplatin in the chloride-deficient carrier fluids were higher than in the chloride-containing carrier fluids such as normal saline or Dianeal®. The oxaliplatin concentration in the hypotonic 0.45% half saline showed the highest plasma absorption rate in all carrier fluids. The AUC ratio of normal saline was two times higher than the 5% dextrose solution ($p=0.0102$). Although oxaliplatin in chloride-deficient carrier fluids showed low degradation rates in vitro, AUC ratios of oxaliplatin in the chloride-containing carrier fluids were higher than in the chloride-deficient carrier fluids. This contrary phenomenon can be explained by the role of peritoneal-plasma barriers from the principle of intraperitoneal chemotherapy. The longer stay of oxaliplatin in the peritoneal-plasma barrier is correlated with the efficacy during HIPEC. In our results, the efficacy of HIPEC was influenced not by oxaliplatin concentration in the peritoneal fluid but by plasma. Although there was a relatively higher rate of intact oxaliplatin in the chloride-deficient carrier solution, our results showed that the rapid plasma clearance of oxaliplatin in the hypotonic chloride-deficient carrier solution decreased AUC ratios. In addition, because the degradation rate of oxaliplatin is less than 10% during HIPEC of 30 minutes, our results can suggest that isotonic and chloride-containing carrier fluids such as normal saline or Dianeal® can be a better choice as a HIPEC carrier fluid than the 5% dextrose solution.

HIPEC has pharmacologic principles that provide regionally intensified antineoplastic drug concentration in the peritoneal cavity and promote tumor cell

penetration with a prolonged presence in the peritoneal-plasma barrier.[10] Based on the anatomical structures of the peritoneum, anticancer drugs that have large molecular weight (MW) and water insolubility are correlated with a larger AUC ratio and longer stay in the peritoneal cavity.[6] The intercellular gaps of the mesothelium are larger than those in the endothelium; therefore, large molecules that cannot pass through endothelial layers do penetrate mesothelial layers. The molecular weight of oxaliplatin is 397.3 g/mol, which is smaller than both the anticancer drugs paclitaxel (MW=853.9 g/mol) and docetaxel (MW=861.9 g/mol).[11] In addition, the logarithm ratio of the partition coefficient (log P) of oxaliplatin is -0.47, which tends to be water-soluble. Therefore, these pharmacologic characteristics of oxaliplatin are not inherently suitable for enhancing the effect of IP chemotherapy, with the exception of water solubility, which is a useful characteristic for circulating solutes during HIPEC. However, importantly, our results demonstrate that the use of a lipid carrier solution increased the AUC ratio and reduced the plasma absorption rate. Although the oxaliplatin AUC_{fluid} was not significantly different among carrier fluids, our data showed that a lipid carrier solution has advantages, controlling the permeability of the endothelial layers and reducing the plasma absorption rate during HIPEC. This could be a result of hydrophobic lipid particles that are resistant to traversing the plasma membrane of endothelial cell layers.

According to the comparison of carrier fluids between lipophilicity and hydrophilicity, the oxaliplatin AUC_{fluid} was not significantly different among carrier fluids. However, the AUC_{plasma} of the lipid solution was lower than that of the 5% dextrose solution. In addition, in the comparison between Dianeal® and 5% dextrose solution, the AUC_{plasma} in the Dianeal® group was marginally lower than with the 5% dextrose solution ($p=0.070$). Although there was no statistical difference in the peritoneal/plasma AUC ratio between the 5% dextrose solution and Dianeal® ($p=0.125$), the average peritoneal/plasma AUC ratio of Dianeal® was about 2.2 times higher than the 5% dextrose solution. Thus, in this study, the lipophilicity of a carrier

fluid seemed to have an advantage in terms of reducing plasma absorption and increasing the peritoneal/plasma AUC ratio compared with hydrophilic carrier fluids.

In HIPEC using oxaliplatin, the 30-minute duration is regarded as clinically suitable considering the half-life of oxaliplatin and systemic toxicities. Elias et al. reported that the plasma concentration of platinum in oxaliplatin reaches the peak level within 30 minutes of the beginning of HIPEC.[32] However, since this study was the first experiment to use a lipophilic carrier solution for oxaliplatin-HIPEC, the HIPEC duration was considered to be the time in which to fully evaluate the pharmacologic properties of the lipid carrier solution. As the mortality numbers increased in the lipid carrier solution after 60 minutes of HIPEC despite pre-hydration, HIPEC was performed for 60 minutes in this study.

In comparison with the pharmacological effects of oxaliplatin in the chloride-containing solutions, our results support the effectiveness of Dianeal®, a chloride-containing isotonic solution. The chloride concentration of Dianeal® PD-2 solution is 96 mmol/L, whereas the 5% dextrose solution is 0 mmol/L. The 20% lipid solution (Lipision®) is composed of purified soybean oil, purified phospholipid and glycerin. Dianeal® had advantages for reducing the plasma absorption of anticancer drugs compared with the 5% dextrose solution, when performing oxaliplatin HIPEC. In addition, the structural instability of oxaliplatin in the chloride-containing solutions during HIPEC can be regarded as acceptable because an earlier report of Mehta et al. supported the assessment that the degradation rates of oxaliplatin were limited to within 10-15% of those found in the chloride-containing HIPEC carrier solution.[20] It is also expected that peritoneal dialysis solutions have advantages in terms of reducing postoperative complications such as electrolyte imbalance and metabolic disturbance. Therefore, peritoneal dialysis solutions might be an optimal choice for improving peritoneal-plasma AUC ratios when performing oxaliplatin HIPEC.

Our study's results also showed that the AUC ratio of a lipid carrier solution was larger than those of other carrier solutions. However, there are some limitations in using lipid carrier solutions in clinical applications for HIPEC. Lipision®, which was used in this study, is a fat emulsion. Although the lipid layers of Lipision® retard plasma absorption rates of anticancer drugs during HIPEC, the hypertonicity and electrical resistance of these lipid layers can inhibit the permeability of peritoneal-plasma barriers. In addition, according to the pharmacokinetic principles of HIPEC, longer duration in the peritoneum delays recirculation of the tumor core.[6] Because the efficacy of HIPEC is related to sustained peritoneal drug concentrations, as well as drug infiltration into the tumor core, this contrary phenomenon should be considered when selecting an optimal IP chemotherapeutic agent. In our results, although the lipid carrier solution prolonged peritoneal occupancy as well as reduced the plasma absorption rate, the hydrophobicity of the lipid solution might be inadequate to recirculate into the tumor core from the capillary vessels and to increase cytotoxicity. Furthermore, because the bioavailability of anticancer agents is assessed from the release rate of an entrapped drug in lipid layers, it can be questioned whether anticancer agents mixed in a lipid carrier solution have complete tumor cell cytotoxicity during HIPEC.[10,24,25] The release rate of anticancer drugs in the lymphatic channels and the risk of fat embolism are also to be considered when a lipid carrier solution is used during HIPEC.

This study has several limitations, including a small sample-sized experiment in the animal model. In addition, there is a lack of investigation into both the cytotoxic effects and the rate of the lymphatic spread of anticancer drugs during HIPEC with a lipophilic carrier solution. Naïve oxaliplatin is known to have less cytotoxicity than the dichloro-platinum compound $Pt(dach)Cl_2$, which is an active form that is transformed in chloride-containing media.[24,25] Since our study measured the platinum concentration of oxaliplatin during HIPEC, we experienced some limitations in assessing the biotransformation of oxaliplatin according to HIPEC carrier solutions. Further studies are required to measure the concentration of oxaliplatin

transformation, in order to understand both the structural instability and the cytotoxicity of oxaliplatin depending on different HIPEC carrier solutions.

The ideal carrier fluid was regarded as having the following properties: slow clearance rate from the peritoneal cavity, sustained high IP volume, adequate exposure of peritoneal surfaces, and absence of adverse effects during HIPEC.[23] Further examinations are needed because of the pharmacologic disparity between its characteristics and the peritoneal-plasma barriers.

V. CONCLUSION

The chloride-containing carrier fluids showed higher pharmacological efficacy than chloride-deficient carrier fluids during HIPEC. The AUC ratios of chloride-containing carrier fluids were about two times higher than non-chloride-containing carrier fluids during in vivo study. In addition, the degradation rates of oxaliplatin were acceptable that they were less than 15% during in vitro study lasting 30 minutes at 43℃. Because transformed oxaliplatin in the chloride-containing carrier fluid can be more cytotoxic than the native form, the use of chloride-containing carrier fluids such as normal saline or Dianeal® has advantages in HIPEC. Therefore, we concluded that the most important factor for pharmacological efficacy during HIPEC is to enable it to decrease the plasma absorption rates of anticancer drugs during HIPEC. In addition, the chloride-containing carrier fluids are more beneficial to use for oxaliplatin-based HIPEC with pharmacological efficacy as well as overcoming postoperative adverse events caused by hypotonic carrier fluids.

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ABSTRACT (IN KOREAN)

Oxaliplatin 를 사용하는 복강내 온열항암화학요법에서 관류액의 약리학적 특성 분석

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박은정

연구의 배경: 대장암 복막전이 치료를 위한 복강내 온열항암화학요법에 있어 관류액은 항암제의 용해성, 복강내 고른 분포, 혈액내 흡수 및 약제의 안정성 유지를 위해 중요한 역할을 한다. 특히 Oxaliplatin 은 염소가 포함된 관류액에 용해될 때 화학적 구조의 변형으로 인해 불안정성을 지니는 약리학적 특성을 갖고 있다. 본 연구에서는 Oxaliplatin 을 사용하는 복강내 온열항암화학요법에 있어 보다 효과적이고 안정성을 지니는 관류액에 대해 살펴보고 수용성 및 지용성을 지니는 관류액에서 Oxaliplatin 을 사용한 복강내 온열항암화학요법의 약리학적 특성에 대해 분석하였다.

재료 및 방법: Oxaliplatin 을 염소함량이 다른 관류액(0.9% 식염수, 0.45% 식염수, 포도당용액, 인산완충액, 복막투석액, 염소를 제거한 복막투석액)에 섞어 25 도, 37 도, 43 도 온도에서 72 시간동안 Oxaliplatin 의

남아있는 농도를 고성능액체크로마토그래피를 통해 측정해 Oxaliplatin 의 분해율을 용액 및 온도별 비교하였다. 이후 각 그룹당 쥐를 호흡마취 시킨 후 각각의 관류액에 대한 Oxaliplatin 을 사용한 복강내 온열항암화학요법을 43 도 온도에서 60 분간 시행하여 혈장 및 복강내 관류액의 Oxaliplatin 농도를 측정해 관류액 종류에 따른 복막흡수율을 비교하였다. 지용성 관류액에 대해서는 20%의 지방유제를 사용해 복강내 온열항암화학요법을 시행해 포도당 및 복막투석액을 사용했을때와 약리학적 특성을 비교하였다.

결과: 25 도, 37 도 43 도 온도조건에서 염소가 포함되어 있지 않은 관류액은 염소가 포함된 관류액에 비해 Oxaliplatin 의 분해율이 낮았다. 그러나 43 도 온도에서 30 분동안 측정한 Oxaliplatin 은 15% 미만의 분해율을 보였고 온도가 올라갈수록 Oxalplatin 분해율이 높아지는 경향을 보였다. 그러나 복강내 온열항암화학요법을 시행한 동물실험에서 관류액에 따라 복강내 순환하는 용액에 남은 Oxaliplatin 의 농도는 관류액간에 차이가 없었으며, 염소가 함유된 관류액을 사용한 경우 Oxaliplatin 의 혈장내 흡수율이 낮아 염소가 함유되지 않은 관류액에 비해 보다 높은 복막흡수율을 보였다. 또한 지방유제를 관류액으로 사용한 복강내 온열항암화학요법에서도 지방유제는 수용성 용액에 비해 혈장 내 Oxaliplatin 흡수율을 낮게하여 복막흡수율을 높이는 결과를 보였다.

결론: 본 연구 결과 염소가 함유된 관류액에서의 Oxaliplatin 의 분해율은 15% 미만으로 낮으며 Oxaliplatin 을 사용한 복강내 온열항암화학요법에서 염소가 함유된 관류액의 복강내 흡수율은 포도당용액보다 높아 임상적으로 생리식염수나 복막투석액을 사용하는 복강내 온열항암화학요법이 보다 효과적일 것으로 여겨진다.

핵심되는 말: 복막전이, 복강내 온열항암화학요법, 항암제, 약리학적 작용, 관류