Safety and Health at Work 14 (2023) 237–242

Contents lists available at ScienceDirect

Safety and Health at Work

journal homepage: www.e-shaw.net

Original article

Occupational Exposure during Intraperitoneal Pressurized Aerosol Chemotherapy Using Doxorubicin in a Pig Model

Wongeon Jung [1], Mijin Park [1,2], Soo Jin Park [3], Eun Ji Lee [4], Hee Seung Kim [5], Sun Ho Chung [6], Chungsik Yoon [1,7,*]

[1] Department of Environmental Health Sciences, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[2] Wonjin Institute for Occupational & Environmental Health, Seoul, Republic of Korea
[3] Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Republic of Korea
[4] Department of Obstetrics and Gynecology, Chung-Ang University Hospital, Seoul, Republic of Korea
[5] Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Republic of Korea
[6] Bio-Center, Gyeonggido Business & Science Accelerator (GBSA), Suwon, Republic of Korea
[7] Institute of Health and Environment, Seoul National University, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 6 September 2022
Received in revised form
17 March 2023
Accepted 7 April 2023
Available online 11 April 2023

Keywords:
Doxorubicin
Occupational exposure
PIPAC
Pressurized intraperitoneal aerosol chemotherapy

ABSTRACT

Background: This study evaluated occupational exposure levels of doxorubicin in healthcare workers performing rotational intraperitoneal pressurized aerosol chemotherapy (PIPAC) procedures.
Methods: All samples were collected during PIPAC procedures applying doxorubicin to an experimental animal model (pigs). All procedures were applied to seven pigs, each for approximately 44 min. Surface samples ($n = 51$) were obtained from substances contaminating the PIPAC devices, surrounding objects, and protective equipment. Airborne samples were also collected around the operating table ($n = 39$). All samples were analyzed using ultra-high performance liquid chromatography-mass spectrometry.
Results: Among the surface samples, doxorubicin was detected in only five samples (9.8%) that were directly exposed to antineoplastic drug aerosols in the abdominal cavity originating from PIPAC devices. The telescopes showed concentrations of 0.48–5.44 ng/cm^2 and the trocar showed 0.98 ng/cm^2 in the region where the spraying nozzles were inserted. The syringe line connector showed a maximum concentration of 181.07 ng/cm^2, following a leakage. Contamination was not detected on the surgeons' gloves or shoes. Objects surrounding the operating table, including tables, operating lights, entrance doors, and trocar holders, were found to be uncontaminated. All air samples collected at locations where healthcare workers performed procedures were found to be uncontaminated.
Conclusions: Most air and surface samples were uncontaminated or showed very low doxorubicin concentrations during PIPAC procedures. However, there remains a potential for leakage, in which case dermal exposure may occur. Safety protocols related to leakage accidents, selection of appropriate protective equipment, and the use of disposable devices are necessary to prevent occupational exposure.

1. Introduction

Peritoneal metastasis from solid tumors is associated with a poor prognosis and quality of life. The current treatment strategies are limited to systematic chemotherapy and palliative care. However, innovative chemotherapy technologies have been shown to be effective and have clinical advantages. The recent advent of cytoreductive surgery has led to the application of hyperthermic intraperitoneal chemotherapy as a multimodal therapy to eliminate residual cancer cells within the abdominal cavity [1]. However, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are associated with low drug penetration, side effects, and occupational exposure to healthcare workers [2,3]. To address these limitations, a novel pressurized intraperitoneal aerosol

Wongeon Jung: https://orcid.org/0000-0003-0570-2485; Mijin Park: https://orcid.org/0000-0003-2449-3965; Soo Jin Park: https://orcid.org/0000-0002-7382-230X; Eun Ji Lee: https://orcid.org/0000-0001-6464-8955; Hee Seung Kim: https://orcid.org/0000-0003-1238-7604; Sun Ho Chung: https://orcid.org/0000-0003-1536-4643; Chungsik Yoon: https://orcid.org/0000-0001-7822-0079
* Corresponding author. Graduate School of Public Health, Seoul National University (GSPH, SNU), 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea.
E-mail address: csyoon@snu.ac.kr (C. Yoon).

2093-7911/$ – see front matter
https://doi.org/10.1016/j.shaw.2023.04.002

chemotherapy (PIPAC) technology has been proposed [4], which improved the feasibility, safety, and cell penetration depth of the drug [5].

The risk of occupational exposure via air or surface contamination during PIPAC procedures remains controversial. This form of chemotherapy involves inflation of the peritoneum with carbon dioxide (CO_2), followed by the aerosolization of liquid-phase pharmaceutical substances such as antineoplastic drugs under high pressure. During this process, aerosolized drugs could diffuse into the air, contaminate surfaces, or leak from PIPAC devices [6,7]. Insufficient assessments of healthcare worker exposure to dangerous drugs during PIPAC procedures have been conducted. To date, there are few studies that have examined doxorubicin levels in air and surface samples.

Doxorubicin is among the most frequently used drugs in PIPAC procedures; it has been known as a substance that was reported the evidence of carcinogenicity in animal, but the evidence for humans is insufficient (Group 2A) by the International Agency for Research on Cancer [8]. Especially, the carcinogenicity of doxorubicin for human was reported when they were used with some other agents. The other antineoplastic drugs could have serious health effects such as carcinogenicity, teratogenicity, reproductive toxicity, and other organ toxicity at low doses [9,10]; similarly, doxorubicin induces DNA mutations. Doxorubicin has also been reported to cause mucosal inflammation, leukopenia, and dilative cardiomyopathy [2]. Thus, doxorubicin exposure may represent a serious occupational hazard for healthcare workers.

Although several studies have evaluated occupational antineoplastic drug exposure levels during PIPAC procedures, they have mainly focused on platinum compound drug types (e.g., cisplatin or oxaliplatin). In some studies, platinum compounds and doxorubicin were mixed for PIPAC application; however, exposure levels were evaluated only for platinum [11,12]. The only recent study that evaluated doxorubicin detected low concentrations of surface contamination on the floor [13]. Therefore, it is necessary to monitor air and surface contamination levels during PIPAC procedures to obtain comprehensive doxorubicin exposure data, including contamination levels following leakage, device insertion into the abdominal cavity, and air exposure.

Since PIPAC has not been introduced in Republic of Korea, the Korean Rotational Intraperitoneal pressurized Aerosol chemotherapy (KoRIA) Trial Group has developed PIPAC, and rotational intraperitoneal pressurized aerosol chemotherapy (RIPAC) to improve drug delivery [14–16]. Thus, we evaluated potential occupational exposure to doxorubicin during PIPAC procedures by analyzing air and surface samples collected following PIPAC procedures involving doxorubicin.

2. Materials and methods

2.1. PIPAC and RIPAC using doxorubicin

The Institutional Animal Care and Use Committee of Seoul National University Hospital approved this study in advance (No. 18-0051-S1A0). PIPAC and RIPAC are applied in three steps: preparation, spraying and waiting, and a finishing step. During the procedures observed in this study, the treatment consisted of 3.5 mg of powdered doxorubicin dissolved in 50 mL of 0.9% sodium chloride (NaCl). PIPAC and RIPAC were applied to three or four female pigs, which were performed by seven healthcare workers (two surgeons, four nurses, and one veterinarian). In the first step, a doxorubicin solution was prepared in the operating room and injected into PIPAC and RIPAC syringe. In the second step, healthcare workers left the room, and remote spraying was conducted at a flow rate of 30 mL/min for 3 min. After waiting for 30 min for the drug to be absorbed in the abdominal cavity, healthcare workers returned to the room and finished the procedure in the final step. The total procedure time was approximately 50 min.

Two 12-mm trocars (Transport-TR12F; Dalimsurg NET Inc., Seoul, Republic of Korea) were used to inject the drug into the pig abdominal cavity, and CO_2 insufflation of the abdominal cavity was maintained at 12 mmHg. Doxorubicin solution was sprayed from the syringe through DreamPen® (Dreampac Corp., Wonju, Republic of Korea), a nebulizer for aerosolization. During PIPAC and RIPAC procedures, a telescope was used to identify the inside of the abdominal cavity. The internal CO_2 and residual aerosol antineoplastic drug were discharged through an air waste system equipped with a glass microfiber impregnated with a carbon layer (Laparo Clear Smoke Filtration Kit; pore size, 0.027 μm; diameter, 50 mm; GVS Life Science, Bologna, Italy).

The volume of the operating room was approximately 98.1 m^3. The operating room contained two air supply vents in the ceiling and one air exhaust vent in each of the four corners. The flow rate (m^3/min) of the air supply and exhaust, measured using a direct-reading balometer (Alnor EBT-731, TSI Inc., Shoreview, MN, USA), was 30.2 m^3/min and 15.1 m^3/min, respectively.

2.2. Surface and air sampling

Surface samples were collected mainly from PIPAC and RIPAC devices such as trocars, nebulizers, telescopes, lines, and connectors, as well as from surfaces around the operating table (Fig. 1). Surface sampling was conducted by wiping with ashless filter paper (Whatman 42; diameter, 55 mm; GE Healthcare Life Science, Marlborough, MA, USA) wetted with a wiping solution consisting of 10% acetonitrile, 25% methanol, and 65% Milli-Q water buffered to pH 6.0 [17–19]. The samples were folded and placed in 50-mL vials, which were transported to the laboratory at approximately −4°C to prevent sample loss.

Air samples were collected using a nitrocellulose membrane filter (diameter, 47 mm; pore size, 0.45 μm; GVS Life Science) with a high-flow pump sampler (SARA-5100; KEMIK Corp., Seoul, Republic of Korea) at a flow rate of approximately 20 L/min, calibrated by an airflow calibrator (Bios Drycal, Mesa Laboratories, Lakewood, CO, USA) before and after measurement [20]. Air sampling was conducted at the height of 1.5 m from the floor where healthcare workers were stationed around the operating table; the sampling time was 50 ± 5 min, including during drug preparation, syringe injection, and air waste management.

2.3. Sample analysis

Analytical methods for substance quantification were applied depending on the filter type. A stock solution of doxorubicin was dissolved in 50% high-performance liquid chromatography (HPLC)-grade methanol (purity >99.9%; Burdick and Jackson, Muskegon, MI, USA) to a concentration of 1 mg/mL and then diluted with 100% methanol to prepare a standard solution. The prepared standard solution was diluted to 5, 10, 20, 50, and 100 ng/mL to construct a linear calibration curve (R^2 = 0.9984–0.9996). Each sample collected for doxorubicin analysis, including used nitrocellulose filters and Whatman filter paper, was placed in a 50-mL tube, extracted with 10 mL and 20 mL of methanol, respectively, and then subjected to sonication for 1 h [21,22]. Centrifugation was performed at 12,000 rpm for 5 min to collect the supernatant. Then, 2-μL aliquots of each sample were injected into the ultra-high-performance liquid chromatograph-tandem mass spectrometer (UPLC-MS/MS; Nexera X2, Shimadzu Scientific Corp., Kyoto, Japan) following the analytical protocols. An Acquity BEH C18 column (1.7 μm; 50 × 2.1 mm; Agilent Technologies Inc., Santa Clara, CA,

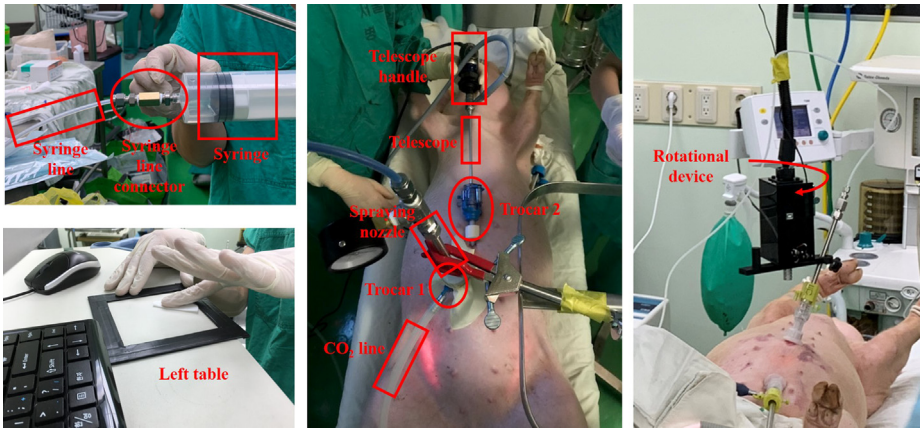

Fig. 1. Surface sampling locations.

USA) was used for UPLC-MS/MS, and quantification was performed using the multiple reaction monitoring modes. The limit of detection (LOD) was calculated by multiplying the standard deviation of the intercept of the calibration curve by 3.3 and dividing by the mean slope, which was nitrocellulose filter 12.8 ng/sample and filter paper 25.6 ng/sample, respectively. The LOD of the air sample was 14.4 ng/m^3 by dividing 12.8 ng/sample by the average amount of air collected. In the case of surface samples, the LOD was 0.16 ng/cm^2 by dividing 25.6 ng/sample by the average of wiped surface area. Here, not detected (ND) was defined as no peak appearing on the chromatograph of the analytical instrument. The mass spectrometer was set to positive ion detection mode. All samples were analyzed at least three times, and the average was calculated. The recovery test was conducted three times at concentrations of 10, 50, and 100 ng/mL using each filter, and the average recovery was calculated by repeating the analysis three times at each concentration. The nitrocellulose filters (air samples) had a recovery range of 86.3–99.7%, and that of the filter papers (surface samples) was 65.1–79.3%.

2.4. Statistical analysis

All concentration data are expressed as arithmetic means with the standard deviation (SD). Descriptive statistics were calculated using the SPSS software (version 25, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Surface contamination levels

A total of 51 surface samples were collected from PIPAC and RIPAC devices ($n = 25$), surrounding objects ($n = 19$), and personal protective equipment ($n = 7$). Among these, five samples were contaminated with doxorubicin, whereas the other samples were not contaminated (Table 1). Among the contaminated PIPAC and RIPAC devices, the syringe line connectors, which connect the syringe to the drug flow line, had the highest concentration of doxorubicin (181.07 ng/cm^2). This result was caused by an antineoplastic drug leak due to incomplete connection. Samples collected from telescopes inserted into the abdominal cavity, which were directly exposed to aerosols, reached doxorubicin concentrations of 0.48–5.44 ng/cm^2. One trocar sample, collected where the spraying nozzle was inserted, was below the doxorubicin detection limit (0.16 ng/cm^2), and another, collected at the telescope insertion site, was 0.98 ng/cm^2. No contamination was detected on surrounding objects or personal protective equipment. Most samples were collected around the operating table; these included tables, operating table lighting, trocar holders, a precessional motion device, and entrance doors. No contamination was detected on the gloves or shoes of the surgeons who performed PIPAC and RIPAC.

3.2. Airborne contamination levels

During PIPAC and RIPAC, doxorubicin was not detected in any of the samples ($n = 39$), regardless of the procedure conditions (Table 2). Doxorubicin was also not detected in samples collected around the operating table (near surgeons, nurses, or anesthesiologists), entrance doors, or the outer corridor.

Table 1
Surface contamination levels of doxorubicin

Type	Sampling location	*N*	Doxorubicin concentration (ng/cm^2)
PIPAC and RIPAC device	Telescope	5	ND*
			ND
			5.44
			0.48
			1.76
	Trocar 2	5	ND
			ND
			ND
			ND
			0.98
	Trocar 1	2	ND
			< LO†
	Syringe line connector	2	181.07
			ND
	CO_2 line	2	ND
	Syringe line	3	ND
	Telescope line	1	ND
	Telescope controller	4	ND
	Telescope line	1	ND
Surrounding objects	Table to the right of operating table	1	ND
	Table to the left of operating table	6	ND
	Operating table lighting	5	ND
	Entrance door	3	ND
	Trocar 1 holder	3	ND
	Precessional motion device	1	ND
PPE	Surgeons' gloves	4	ND
	Surgeons' shoes	3	ND

Abbreviations: LOD, limit of detection; ND, not detected; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PPE, personal protective equipment; RIPAC, rotational intraperitoneal pressurized aerosol chemotherapy.
*The limit of detection of doxorubicin was 0.16 ng/cm^2; the average recovery rate was approximately 0.71.
* The limit of deection of doxorubicin was 0.16 ng/cm^2; the average recovery rate was approximately 0.71.
† ND (Not detected) means that doxorubicin was not identified in chromatograph.

Table 2
Airborne doxorubicin concentration detected following pressurized intraperitoneal aerosol chemotherapy (PIPAC) and rotational intraperitoneal pressurized aerosol chemotherapy (RIPAC)

Procedure	Swine type†	N‡	Treatment types	Sampling time (min)	Air volume (L)§	Concentration (ng/m³)
				AM ± SD	AM ± SD	
1	Large	6	PIPAC	58.3 ± 4.2	1166.7 ± 83.6	ND‖
2	Large	6	RIPAC	43.8 ± 3.7	876.7 ± 74.2	ND
3	Small	6	RIPAC	39.2 ± 4.5	783.3 ± 89.8	ND
	Large	5	PIPAC	39.6 ± 0.9	792.0 ± 17.9	ND
	Large	5	RIPAC	39.6 ± 0.9	792.0 ± 17.9	ND
4	Large	6	RIPAC	43.0 ± 6.5	860.0 ± 129.6	ND
	Large	5	PIPAC	45.6 ± 1.3	912.2 ± 6.8	ND
Total¶		39		44.4 ± 7.4	887.2 ± 147.3	ND

Abbreviations: AM, arithmetic mean; ND, not detected; SD, standard deviation.
† Swine size was classified as large (≥40 kg) or small (<40 kg).
‡ Includes all samples collected around the operating tables, entrance doors, and outer corridors.
§ Air volume (L) was calculated by multiplying the average flow rate (20 L/min) by the sampling time (min).
¶ Total showed the number of samples (N) was the sum, and sampling time (min) or air volume (L) was arithmetic mean and standard deviation.
‖ Total showed the number of samples (N) was the sum, and sampling time (min) or air volume (L) was arithmetic mean and standard deviation.

4. Discussion

In this study, we assessed air and surface contamination following PIPAC and RIPAC procedures applied to a pig model. As a result, we detected surface contamination with doxorubicin in 5 of 51 surface samples obtained by wiping, and these were mainly collected from relevant devices directly exposed to aerosols in the abdominal cavity. Even though the risk of drug leakage might be greater in RIPAC than in PIPAC due to the conical pendulum motion, the air in the operating room was not contaminated during the procedures, and doxorubicin was not detected in the air following the two procedures.

Certain equipment, including the telescope, trocar, and syringe line connector, was contaminated following PIPAC and RIPAC procedures. Since the telescope and the trocar were inserted into the abdominal cavity, they bear a greater risk of surface contamination through exposure to the aerosolized antineoplastic drug. A drug leak occurred via droplet outflow due to incomplete coupling of the syringe containing doxorubicin to the spraying nozzle; the level of contamination was 181.07 ng/cm^2. Prior to the experiment, we assumed that there would be some correlation between airborne and surface samples, but this was not the case. That is, even when the concentration of the surface sample was high (181.07 ng/cm^2), it was not detected in the air sample. The reason seems to be that during the PIPAC procedure, the leak was in the liquid state of droplets, and it was difficult to volatilize into the air due to its low volatility (molar mass 543.5 g/mol), and also because the ventilation was continuous as described in the method.

To date, few studies have attempted to evaluate occupational exposure of healthcare workers during PIPAC procedures. Some such studies have applied doxorubicin with cisplatin or oxaliplatin as platinum compounds for PIPAC chemotherapy [2,11–13]. However, only one recent study examined surface contamination with doxorubicin; they reported a doxorubicin concentration level of 0.29 pg/cm^2 on the floor around the operating table and a maximum doxorubicin contamination level of 0.03 ng/cm^2 in the nozzle head [13]. Although we did not collect samples from the nozzles used in this study, we detected a maximum contamination level of 5.44 ng/cm^2 on the telescope, which has similar exposure characteristics to the nozzle, as both are inserted directly into the abdominal cavity. Surface contamination was also reported on healthcare workers' protective equipment [13], but this was not detected in the present study.

Doxorubicin was not detected in air samples collected within the operating room during PIPAC procedures. Considering that the limit of detection for doxorubicin was 1.28 ng/mL (10 mL of extract solution), 12.28 ng of doxorubicin per air sample (14.4 ng/m^3) would be required for detection. Exposure assessment studies of PIPAC using other antineoplastic drugs (e.g., oxaliplatin or cisplatin) have reported no air contamination; thus, respiratory exposure appears to be unlikely during PIPAC procedures. However, caution should be exercised at the risk of aerosol leakage from the abdominal cavity while high pressure is maintained. The results of the present study suggest that healthcare workers operating PIPAC procedures are not at risk of inhaling doxorubicin aerosols.

Antineoplastic drugs have varying toxicity [23]; doxorubicin has been reported to be associated with carcinogenicity and mutagenicity in animals [2]. The oral half-lethal dose (LD_{50}) of doxorubicin has been reported as 570 mg/kg in mice, and it may be associated with harmful acute toxicity, dilative cardiomyopathy, and mucosa inflammation [2]. However, toxic doses have not been established for inhalation. Among the antineoplastic drugs used in PIPAC, an exposure limit has been established only for platinum compounds (0.002 mg/m^3; Occupational Safety and Health Administration [OSHA], National Institute for Occupational Safety and Health [NIOSH], and American Conference of Governmental Industrial Hygienists [ACGIH]) [24]. According to the results of this study, it was considered that the possibility of exposure was low unless it was an event such as leakage. However, all possible exposures must be prepared for precautionary prevention because toxicity information (i.e., exposure limit) for doxorubicin was insufficient.

It is necessary to use precautions in operating room settings throughout PIPAC and RIPAC to prevent aerosolized drugs from leaking from the abdominal cavity. A previous study reported that a self-checklist should be required for all aerosol chemotherapy procedures to avoid contamination from high-pressure injectors, as well as during the preparation, dilution, and handling of the drugs and devices involved in treatment [7]. Even with these checklists, risks may persist, even with the application of controlled operating room technologies, including laminar flow, ventilation, and remote controlling systems [6]. As observed with the leak described in this study, surface contamination can occur due to incomplete coupling of the devices and connector lines through which antineoplastic drugs flow.

Our study has a few limitations. First, we did not assess exposure levels on a task-by-task. For example, tasks such as diluting antineoplastic drugs for inject them into a syringe may present risks. Thus, we sampled many locations within the operating room that have not been sampled in other studies, such as operating table lightning and entrance doors, and we were able to quantify the level of contamination due to a leak during the procedure. Moreover, we evaluated the overall contamination levels at various locations associated with tasks for PIPAC procedures. The second might be about sampling and analysis. As with many antineoplastic drugs, there is no standardized sampling and analysis method for doxorubicin, such as the NIOSH or ISO method. Doxorubicin is also not a commonly encountered material in the field of industrial hygiene. Therefore, the most appropriate method was selected in this study by referring to the existing literature (17-19). In order to ensure the accuracy of the analysis, the linearity of the standard solution ($R^2 = 0.99$), recovery rate (air sample; 0.95, surface sample: 0.71), and detection limit (air sample: 14.4 ng/m^3, surface

sample: 0.16 ng/cm^2) were measured. Although it was obtained, additional research is needed to ensure the accuracy of sampling and analysis overall.

In this study, we assessed the doxorubicin contamination levels following PIPAC and RIPAC applied to an animal model. Although we detected no air contamination, doxorubicin was detected on the surfaces of relevant devices. We also confirmed the leakage of doxorubicin droplets from connector devices during the preparation, handling, or disposal steps of the procedures, with contamination reaching 181.07 ng/cm^2. Thus, it is important to prevent risks during PIPAC and RIPAC by minimizing human error to the extent possible through the establishment of self-checklists and safety guidelines.

Funding

This research was supported by Seoul National University [No. 800-20180201], the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (BK21 FOUR 5199990214126), and Commercializations Promotion Agency for R&D Outcomes grant funded by the Korea government (the Ministry of Science and ICT) (Project No. 1711177795).

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

The authors deeply appreciate Dreampac Corp. (Wonju-Gangwon, Republic of Korea) and Precision Medicine for Peritoneal Metastasis Corp. (WonjuGangwon, Republic of Korea) for their support in conducting rotational intraperitoneal pressurized aerosol chemotherapy. Moreover, the authors thank members of the Korean Rotational Intraperitoneal pressurized Aerosol chemotherapy (KoRIA) Trial Group, including Hee Su Lee, Junsik Kim (Interdisciplinary Program in Bioengineering, Seoul National University Graduate School, Seoul, Republic of Korea), Sunwoo Park (Department of Plant & Biomaterials science, Gyeongsang National University, Jinju, Republic of Korea), Jiyeon Ham, Gwonhwa Song (Institute of Animal Molecular Biotechnology and Department of Biotechnology, College of Life Sciences and Biotechnology, Korea University, Seoul, Republic of Korea), Ga Won Yim (Department of Obstetrics and Gynecology, Dongguk University Ilsan Hospital, Goyang, Republic of Korea), Seung-Hyuk Shim (Department of Obstetrics and Gynecology, Research Institute of Medical Science, Konkuk University School of Medicine, Seoul, Republic of Korea), Beong-Cheol Kang (Department of Experimental Animal Research, Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea) Suk Joon Chang (Department of Obstetrics and Gynecology, Ajou University School of Medicine, Suwon, Republic of Korea), Whasun Lim (Department of Biological Sciences, Sungkyunkwan University, Suwon, Republic of Korea), Ji Won Park (Department of Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea), and Jung Chan Lee (Department of Biomedical Engineering, Seoul National University College of Medicine, Seoul, Republic of Korea).

References

[1] Giorgio AD, Naticchioni E, Biacchi D, Sibio S, Accarpio F, Rocco M, Tarquini S, Seri MD, Ciardi A, Montruccoli D, Sammartino P. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. Cancer 2008;113(2):315–25. https://doi.org/10.1002/cncr.23553.

[2] Solaß W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol 2013;20:3504–11. https://doi.org/10.1245/s10434-013-3039-x.

[3] Rodier S, Saint-Lorant G, Guilloit J, Palix A, Divanon F, Sichel F, Delépée R. Is hyperthermic intraperitoneal chemotherapy (HIPEC) safe for healthcare workers? Surg Oncol 2017;26:242–51. https://doi.org/10.1016/j.suronc.2017.04.001.

[4] Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc 2012;26:1849–55. https://doi.org/10.1007/s00464-012-2148-0.

[5] Kurtz F, Struller F, Horvath P, Solass W, Bösmüller H, Königsrainer A, Reymond MA. Feasibility, safety, and efficacy of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis: a registry study. Gastroenterol Res Pract 2018:1–8. https://doi.org/10.1155/2018/2743985.

[6] Reymond L, Solass W, Tempfer C, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC). In: Berhardt LV, editor. Advances in medicine and biology, vol. 87. New York: Nova Science Publishers; 2015. p. 159–80.

[7] Giger-Pabst U, Tempfer CB. How to perform safe and technically optimized pressurized intraperitoneal aerosol chemotherapy (PIPAC): experience after a consecutive series of 1200 procedures. J Gastrointest Surg 2018;22:2187–93. https://doi.org/10.1007/s11605-018-3916-5.

[8] International Agency for Research on Cancer [Internet]. IARC monographs on the identification of carcinogenic hazards to humans. World Health Organization. 1987 [cited 2021 Oct 31]. Available from: https://monographs.iarc.who.int/list-of-classifications.

[9] National Institute for Occupational Safety and Health [Internet]. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings (Publication no. 2004-165). Cincinnati (OH): DHHS (NIOSH). 2004 [cited 2021 Oct 31]. Available from: https://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf?id=10.26616/NIOSHPUB2004165.

[10] National Institute for Occupational Safety and Health [Internet]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings (Publication No. 2012-150). Cincinnati (OH): DHHS (NIOSH). 2012 [cited 2021 Oct 31]. Available from: https://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf.

[11] Graversen M, Pedersen PB, Mortensen MB. Environmental safety during the administration of pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pleura Peritoneum 2016;1(4):203–8. https://doi.org/10.1515/pp-2016-0019.

[12] Willaert W, Sessink P, Ceelen W. Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pleura Peritoneum 2017;2(3):121–8. https://doi.org/10.1515/pp-2017-0018.

[13] Roussin F, Taibi A, Canal-Raffin M, Cantournet L, Durand-Fontanier S, Druet-Cabanac M, Balkhi SE, Maillan G. Assessment of workplace environmental contamination and occupational exposure to cisplatin and doxorubicin aerosols during electrostatic pressurized intraperitoneal aerosol chemotherapy. Eur J Surg Oncol 2021;47(11):2939–47. https://doi.org/10.1016/j.ejso.2021.05.020.

[14] Lee HS, Kim J, Lee EJ, Park SJ, Mun J, Paik H, Oh SH, Park S, Ryu S, Lim W, Song G, Kim HS, Lee JC. Evaluation of a novel prototype for pressurized intraperitoneal aerosol chemotherapy. Cancers (Basel) 2020;12:633. https://doi.org/10.3390/cancers12030633.

[15] Mun J, Park SJ, Kim HS. Rotational intraperitoneal pressurized aerosol chemotherapy in a porcine model. Gland Surg 2021;10:1271–5. https://doi.org/10.21037/gs-2019-ursoc-11.

[16] Park SJ, Lee EJ, Lee HS, Kim J, Park S, Ham J, Mun J, Paik H, Lim H, Seol A, Yim GW, Shim S, Kang B, Chang SJ, Lim W, Song G, Kim J, Lee N, Park JW, Lee JC, Kim HS. Development of rotational intraperitoneal pressurized aerosol chemotherapy to enhance drug delivery into the peritoneum. Drug Deliv 2021;28:1179–87. https://doi.org/10.1080/10717544.2021.1937382.

[17] Turci R, Sottani C, Spagnoli G, Minoia C. Biological and environmental monitoring of hospital personnel exposed to antineoplastic agents: a review of analytical methods. J Chromatogr B Analyt Technol Biomed Life Sci 2003;789:169–209. https://doi.org/10.1016/s1570-0232(03)00100-4.

[18] Connor TH, DeBord DG, Pretty JR, Oliver MS, Roth TS, Lees PSJ, Kreig EF, Rogers B, Escalante CP, Toennis CA, Clark JC, Johnson BC, McDiarmid MA. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. J Occup Environ Med 2010;52(10):1019–27. https://doi.org/10.1097/JOM.0b013e3181f72b63.

[19] Connor TH, Zock MD, Snow AH. Surface wipe sampling for antineoplastic (chemotherapy) and other hazardous drug residue in healthcare settings: methodology and recommendations. J Occup Environ Hyg 2016;13(9):658–67. https://doi.org/10.1080/15459624.2016.1165912.

[20] Larson RR. Development and validation of a method for accurate collection and analysis of select antineoplastic contaminants, both in air and on surfaces, and implications for exposure assessment. Ph. D. dissertation. The University of Alabama at Birmingham. ProQuest Information and Learning Company; 2001.

[21] Larson RR, Khazaeli MB, Dillon HK. Development of an HPLC method for simultaneous analysis of five antineoplastic agents. Appl Occup Environ Hyg 2003;18(2):109–19. https://doi.org/10.1080/10473220301432.

[22] Bobin-Dubigeon C, Amiand M, Percheron C, Audeval C, Rochard S, Leynia P, Bard J. A new, validated wipe-sampling procedure coupled to LC–MS analysis

for the simultaneous determination of 5-fluorouracil, doxorubicin and cyclophosphamide in surface contamination. J Anal Toxicol 2013;37:433–9. https://doi.org/10.1093/jat/bkt045.

[23] Pan American Health Organization [Internet]. Safe handling of hazardous chemotherapy drugs in limited-resource settings. Washington, DC: Pan American Health Organization. 2013 [cited 2021 Oct 30]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=24983&Itemid=&lang=en.

[24] Murff SJ. United States Concensus Occupational Exposure Level(s)/Limits for Cytotoxic Drugs. In: Murff SJ, editor. Safety and Health Handbook for Cytotoxic Drugs. Lanham (MD): Government Institutes An imprint of The Scarecrow Press; 2012. 244 p.