Wouter Willaert, Paul Sessink and Wim Ceelen*

Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC)

https://doi.org/10.1515/pap-2017-0018
Received June 17, 2017; accepted July 23, 2017;
previously published online August 12, 2017

Abstract

Background: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has emerged as a novel method to treat extensive, small volume peritoneal metastases. The clinical use of chemotherapy containing aerosols represents a potential occupational health hazard. We report the results of toxicological analysis during the first two clinical PIPAC procedures performed at Ghent University Hospital.

Methods: After extensive preparation and *in vitro* testing, two patients were treated with PIPAC: the first using doxorubicin (2.86 mg in 51.43 mL) and cisplatin (14.28 mg in 164.3 mL), the second using oxaliplatin (182.10 mg in 186.42 mL). A standardized safety checklist was developed and used. Aerosol delivery was combined with electrostatic precipitation (ePIPAC). The following samples were obtained at several time points and locations: environmental air, floor surface wipes, surgeon's gloves, surgeon's hand wipes, circuit filters, and fluid from the water seal collection chamber container placed along the closed aerosol waste evacuating line. Platinum concentration was measured in these samples using voltammetry. Sample collection and analysis were performed by an independent external laboratory.

Results: Platinum was not detected on the four floor locations after both procedures (detection limit 0.02 ng/cm^2). Similarly, no platinum was detected in environmental air during both PIPACs at the surgeon's or anesthesiologist's position (detection limit 4.0–27 ng/m^3). No platinum contamination was detected on the hands, outer pair of gloves, or inner pair of gloves of the surgeon (detection limit 70 and 50 ng respectively). Platinum was not detected on the filters and in the air-seal container liquid.

Conclusions: With adequate preparation and precautions, a clinical PIPAC program can be established without measurable chemotherapy exposure to the operating room environment or healthcare workers.

Keywords: carcinomatosis, occupational, PIPAC

Introduction

Peritoneal metastasis is a defining feature of stage III ovarian cancer and occurs in approximately 13% of gastric cancers, 9% of pancreas cancers, and 8% of colorectal cancers [1–4]. In selected patients, cytoreductive surgery combined with hyperthermic intraperitoneal chemoperfusion (HIPEC) results in a significant survival advantage compared to palliative treatment alone [5, 6]. The morbidity of the combined procedure is, however, considerable, and a substantial proportion of patients have locally irresectable disease [7].

In 2012, Marc Reymond and coworkers proposed, in an animal model, a novel approach to intraperitoneal drug delivery, during which chemotherapy is administered as an aerosol during CO_2 pneumoperitoneum [8]. The aerosol is generated by a high pressure line connected to a nozzle, hence the term pressurized intraperitoneal aerosol chemotherapy or PIPAC. Advantages of this approach include minimal morbidity, efficient drug distribution, and tissue penetration, and the possibility to repeat the procedure which allows for visual and histological assessment of treatment response. In patients with widespread, small volume but unresectable peritoneal metastasis, preliminary clinical experience has demonstrated the safety and antitumor efficacy of PIPAC [9–11]. Recently, the same group proposed to combine nebulization of chemotherapy with electrostatic precipitation using the Ultravision™ system. This device, originally developed to clear smoke from the laparoscopic operating field using an electrostatic force, uses a stainless steel microfilament brush (Ionwand™) which is inserted into the abdominal cavity. A high DC voltage (7.5–9.5 kV, ≤ 10 μA) is applied to the wand resulting in a corona discharge and a stream of negatively charged ions, which attach to suspended

***Corresponding author: Wim Ceelen,** Department of GI Surgery, Ghent University Hospital, route 1275, De Pintelaan 185, 9000, Ghent, Belgium; Cancer research institute Ghent (CRIG), Ghent, Belgium, E-mail: Wim.ceelen@ugent.be
Wouter Willaert, Department of GI Surgery, Ghent University Hospital, route 1275, De Pintelaan 185, 9000, Ghent, Belgium, E-mail: wouter.willaert@ugent.be
Paul Sessink, Exposure Control Sweden AB, Bohus-Björkö, Sweden, E-mail: info@exposurecontrol.nl

particles. These now negatively charged smoke particles are attracted to the positively charged tissue surfaces of the abdominal cavity, which is conferred a weak positive charge by the patient return electrode. In theory, the combination of electrostatic precipitation with PIPAC, termed ePIPAC, could result in better tissue penetration of the aerosol. In a recent porcine model, the addition of electrostatic precipitation to PIPAC resulted in higher tissue concentrations of a tracer substance [12]. The first clinical application in three patients with peritoneal metastases was recently reported, and showed ePIPAC to be technically feasible and well tolerated [13].

A possible drawback of (e)PIPAC is the challenge to safely deliver a chemotherapy aerosol intraperitoneally during laparoscopy, while preventing exposure of the involved healthcare workers. In 2013, the group of Reymond in Bochum performed analytical measurements of air samples during two PIPAC procedures [14]. Two patients were treated with PIPAC using cisplatin (7.5 mg/m^2) and doxorubicin (1.5 mg/m^2); analysis of air samples taken at the place of the surgeon as well as that of the anesthesiologist was unable to detect cisplatin air contamination (detection limit < 0.000009 mg/m^3). Graversen and coworkers from the Odense University Hospital in Denmark recently reported the results of air sample analysis and biological monitoring in two surgeons during and after PIPAC in two patients: one treated with cisplatin and doxorubicin, and the second treated with oxaliplatin [15]. No traces of platinum were found in the air samples (detection limit 0.0001 mg), and blood samples of the surgeons showed no traces of platinum.

Here, we report an additional, comprehensive toxicological analysis including air samples, surface wipe samples, and analysis of surgeon's gloves and hands after clinical PIPAC procedures using cisplatin/doxorubicin and oxaliplatin.

Patients and methods

Description of the standard PIPAC procedure used at Ghent university hospital (Figure 1)

A 12 mm balloon trocar (Applied Medical, Amersfoort, The Netherlands) is inserted and a 12 mmHg pneumoperitoneum is established. A 5 mm balloon trocar (Applied Medical, Amersfoort, The Netherlands) is then placed under direct vision. Any ascites is aspirated, sampled for cytology and/or bacteriology, and its volume is noted. If needed, limited careful adhesiolysis is performed to allow a complete exploration of the peritoneal cavity and to calculate the extent of peritoneal carcinomatosis using the peritoneal cancer index. Particularly, intestinal dilatation from malignant adhesions, a precursor of obstruction to occur erelong, is assessed. Next, to estimate the therapeutic effects of subsequent PIPACS, biopsies of peritoneal nodules marked by clips are taken in both upper and lower abdominal quadrants and digital photographs are obtained throughout the peritoneal cavity.

Next, the electrostatic PIPAC or ePIPAC injection system is installed (Figure 1). A stainless steel brush electrode (Ionwand™) is inserted into the peritoneal cavity and connected with a dedicated catheter that is placed in the generator unit of the Ultravision System (Alesi Surgical, Cardiff, UK). The Ultravision System is turned on after complete nebulization of the chemotherapy. Prevention of exposure of the surgical team to chemotherapy must be guaranteed by preventive measures taken during installation of the ePIPAC injection system. Because maintenance of a leak-free pneumoperitoneum of 12 mm Hg is essential, every potential cause of spread of aerosol from the pneumoperitoneum through the trocars must be evaluated. Therefore, airtight balloon trocars are used; the port of the balloons is closed with a cap; the luer lock of the 5 mm trocar is closed; and the CO_2 inflator tube, which is connected with the 12 mm balloon trocar, has a KV-5 filter (Olympus, Hamburg, Germany) at its

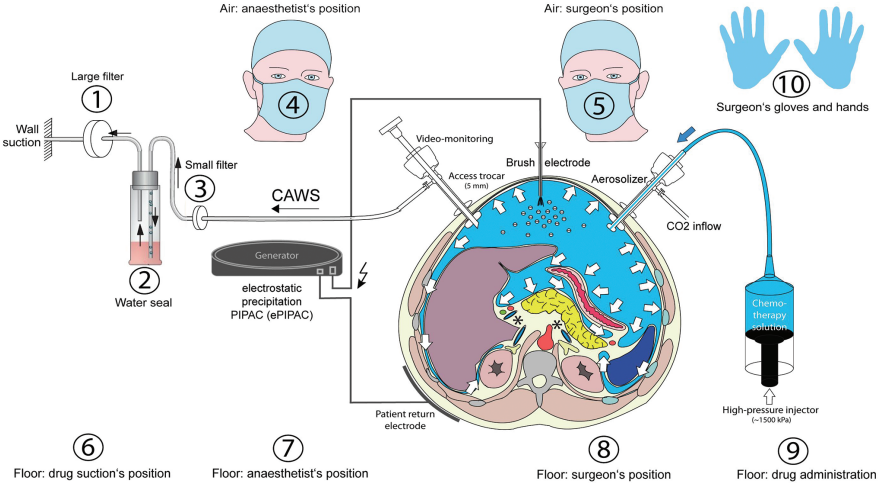

Figure 1: Schematic overview of the ePIPAC setup used at Ghent University Hospital, and of the different samples that were obtained for analysis (1–10). CAWS, closed aerosol waste system.

origin to prevent chemotherapy to enter the insufflator. A high pressure line sealed to the nebulizer (CapnoPen™, Capnomed GmbH, Villingendorf, Germany) and surrounded by a plastic camera cover is used. The nebulizer is then inserted in the 12 mm balloon trocar and secured with the tip just inside the peritoneal cavity. The tip is permanently visualized with a 5 mm 30° camera (EndoEye™, Olympus, Hamburg, Germany) that is placed in the 5 mm balloon trocar and secured with a laparoscopic scope holder (Integra, Zaventem, Belgium, and Cook Medical, Limerick, Ireland). After completion of the ePIPAC procedure, the abdomen is desufflated using a line attached to the 5 mm trocar and equipped with a smoke evacuation filter (MTP Gmbh, Neuhausen Ob Eck, Germany). After CO_2 has passed through this filter, it enters a water seal drainage system (Atrium, Mijdrecht, The Netherlands) that is attached to a wall-mounted suction unit equipped with an infant-pediatric electrostatic filter HME (Medtronic, Brussels, Belgium). This closed waste evacuation assembly is installed before the start of the procedure. After completing the ePIPAC installation, protective sheets are laid out under the injector and next to the patient; team members wear safety glasses and two pairs of gloves (outer pair: Gammex™; inner pair: Gammex Latex Chemo™, both Ansell Healthcare, Brussels, Belgium) and chemotherapy waste containers are provided in the operating room. Then, patient's name and chemotherapy dose on the label of the chemotherapy infusion bag are verified and chemotherapy is completely aspirated through an infusion line into the syringe(s) of the Accutron™ CT-D injector (Euro Medical, Ham, Belgium). Afterward, the end of the syringe is firmly connected to the high pressure line and this connection is surrounded with the plastic camera cover. Then, standard injector settings for ePIPAC are applied (i. e., flow rate of 30 mL/min and maximal pressure of 20 Bar). Before the team leaves the operating room, patients are curarized for 40 minutes; laminar air flow is activated, and an ePIPAC door warning sign ensures that everyone is kept out the operating room during ePIPAC. The locally used ePIPAC safety checklist is provided as Appendix.

Outside the operating room, the injector is activated through a remote control system that allows real-time assessment and control of the established pressure in the nebulizer, the flow rate of the injected chemotherapy and the administration time. A DVI cable that passes through the operating room wall provides real-time laparoscopy imaging and monitoring of the anesthesiology procedure. After complete administration of the chemotherapy (i. e., 5–6 minutes, depending on the dose), the surgeon enters the operating room and activates the Ultravision™ System. A pneumoperitoneum of 12 mmHg is maintained for 30 minutes and promotes tumor penetration of chemotherapy. After ePIPAC, the surgeon desufflates the pneumoperitoneum and laparoscopic incisions are closed.

Description of the clinical procedures performed for the biohazard analysis

On September 23rd 2015, the first two ePIPACs were performed at Ghent University Hospital, Belgium. The first procedure was done in a male 52 years old patient with a diffuse-type signet-ring cell gastric adenocarcinoma. After neoadjuvant treatment with docetaxel, cisplatin and fluorouracil, a total gastrectomy (ypT4aN2M0) was performed followed by radiotherapy (50.4 Gy) and fluorouracil. Metachronous peritoneal carcinomatosis was diagnosed after 10 months and treated with fluorouracil plus leucovorin and irinotecan in combination with ePIPAC using doxorubicin (2.86 mg in 51.43 mL) and cisplatin (14.28 mg in 164.3 mL). The second ePIPAC was performed in a 80 years old male patient with a history of a well-differentiated sigmoid adenocarcinoma (pT4bN2aM0). Adjuvant capecitabine was administered after sigmoid resection. Seventeen months after diagnosis, metachronous peritoneal carcinomatosis was observed and treated with cytoreductive surgery and intraperitoneal chemotherapy. Six months later, ePIPAC with oxaliplatin (182.10 mg in 186.42 mL) was initiated because of recurrent peritoneal disease.

Sample collection

Wipe samples were taken from potentially contaminated floor surfaces in the operating room after the PIPACs. For wipe sampling, Cyto Wipe Kits were used (Exposure Control Sweden AB, Bohus-Björkö, Sweden). The wipe samples were taken with 2 tissues and 17 mL of 0.05 M HCl. The liquid was dripped on the defined surface and spread over the whole surface with one tissue. The second tissue was used to remove the remaining liquid from the surface. Both tissues were collected. A blank sample (2 tissues and 17 mL 0.05 M HCl) was also analyzed. The air samples were collected according to standard procedures. Institute of Occupational Medicine (IOM)-samplers connected to VSS-5 Buck pumps (A.P. Buck Inc., Orlando, USA) were used. Total particulate matter was collected on polytetrafluoroethylene (PTFE) filters (25 mm diameter and 1.0 µm pore size, Whatman, GE Healthcare UK Limited, Little Chalfont, United Kingdom). The air flow was 2.0 L/min. A blank sample (filter) was also analyzed. Both pairs of surgeon gloves were collected and analyzed for contamination. The hands of the surgeon were checked for contamination to establish if the double pair of gloves offered effective protection. The hands were wiped with 3 moist tissues (verfrissingsdoekjes, Kruitvat, Renswoude, The Netherlands). Blank samples (gloves and 3 moist tissues) were also analyzed. To ascertain that the results of the monitoring study were not influenced by previous working activities, a cleaning was performed before the first PIPAC, and wipe samples were collected before and after cleaning. Stationary air samples were collected during the night before the PIPAC to measure background levels of platinum in the operation room.

Sample storage, preparation and analysis

After sampling and during transport to the lab, all samples were stored at room temperature followed by storage at -20 °C until sample preparation and analysis.

A known volume of 0.5 M HCl was added to the wipe samples, gloves, tissues of the hands, and the filters followed by extraction. Next, 0.5 mL extract or water seal liquid (no extraction needed) was destructed with hydrogen peroxide and hydrogen acid using UV light. During this process, platinum containing cytostatic drugs such as cisplatin and oxaliplatin but also other platinum containing compounds are converted into platinum (PT) ions [12]. Hence, it is very important that no contamination is observed in the environment from previous surgical activities before the PIPAC as this could

negatively influence the results. Platinum was finally analyzed with voltammetry on a Computrace (Metrohm Ltd, Herisau, Switzerland) [16]. The results were corrected for potential background values of platinum (compounds) being present in the environment but who were not from platinum containing drugs. The detection limit for platinum was set at 0.5 ng/mL HCl extract.

Results

Platinum was not detected on the four floor positions after both PIPACs (Table 1). This was also the case for the background testing before cleaning and before PIPAC 1 indicating no contamination before the start of PIPAC 1. The limit of quantification was 0.02 ng/cm^2. Platinum was not detected in environmental air during both PIPACs (Table 2). This was also the case for the background testing after cleaning the day before indicating no platinum in environmental air before the start of PIPAC 1. The limit of quantification depending on the air volume collected was between 4.0 and 27 ng/m^3.

Platinum was not detected on the hands, and the outer and inner pair of gloves of the surgeon (Table 3). The limit of quantification was 70 and 50 ng, respectively. Platinum was not detected on the filters and in the liquid of the water locks (Table 4).

Discussion

The perioperative use of cytotoxic agents demands close attention to the occupational health risks of the involved staff. Based on *in vitro* studies, animal experimentation, and epidemiological data, the International Agency of Research on Cancer (IARC) classifies some cytotoxic agents in Group 1 (carcinogenic to humans; includes chlorambucil and cyclophosphamide), Group 2A (probably carcinogenic to humans; includes cisplatin and doxorubicin), and Group 2B (possibly carcinogenic to humans; includes mitomycin-C) [17]. There are no published epidemiological or experimental data on the carcinogenicity of oxaliplatin, and it is not listed by the IARC. Nevertheless, given the similarity to cisplatin in structure and DNA interaction, a similar degree of carcinogenicity is probable. The health risks of occupational exposure to cytotoxic drugs have been documented. A recent meta-analysis showed a 67% higher frequency of micronuclei in peripheral lymphocytes (a marker of genome toxicity) in exposed health care workers compared to controls [18].

The results from studies investigating the occupational hazards for personnel involved in HIPEC procedures have been recently reviewed [19]. In summary, none of the included studies could detect platinum or mitomycin C in urine or plasma of health care workers, or in air samples. Villa and coworkers identified the operating table, operating room floor, and surgeon's overshoes as the most important sources of contamination after open HIPEC with oxaliplatin [20].

Protection of the health care personnel and working environment becomes even more critical when, during PIPAC, chemotherapy is administered as an aerosol. Monitoring of surface contamination by wipe sampling, measuring glove and skin contamination is rather easy to perform and is a standard procedure in many hospitals where cytostatic drugs are prepared and administered. Monitoring is a tool to evaluate routines, procedures and cleaning to prevent environmental contamination and potential exposure to hazardous drugs known to cause adverse health effects [21].

The first safety analysis of the procedure was reported by Solass and colleagues in 2013 [14]. Two patients were treated with PIPAC using cisplatin (7.5 mg/m^2) and doxorubicin (1.5 mg/m^2); analysis of air samples taken at the place of the surgeon as well as that of the anesthesiologist was unable to detect cisplatin air

Table 1: Analysis of surfaces for presence of platinum (PT).

Description of the surface[a]	PT, ng/mL HCl[b]	PT, ng/cm^2	PT, ng/mL HCl[b]	PT, ng/cm^2	PT, ng/mL HCl[b]	PT, ng/cm^2	PT, ng/mL HCl[b]	PT, ng/cm^2
	Background before cleaning		Before PIPAC1		After PIPAC 1 before cleaning		After PIPAC 2 before cleaning	
Floor surgeon	ND	< 0.02	ND	< 0.02	ND	< 0.02	ND	< 0.02
Floor drug administration	ND	< 0.02	ND	< 0.02	ND	< 0.02	ND	< 0.02
Floor drug suction equipment	ND	< 0.02	ND	< 0.02	ND	< 0.02	ND	< 0.02
Floor anesthesiologist	ND	< 0.02	ND	< 0.02	ND	< 0.02	ND	< 0.02

[a]Surface area 4900 cm^2. [b]Total extraction volume 160 mL. ND, not detected (< 0.5 ng/mL HCl).

Table 2: Analysis of environmental air samples for the presence of platinum (PT) .

Location[a]	Sampling time, min	Air collected, L	Total extraction volume HCl, mL	PT, ng/mL HCl	PT, ng/m^3
Left of surgeon (stationary)	545	1090	10	ND	< 4.6
Drug administration (stationary)	467	932	10	ND	< 5.4
Drug suction equipment (stationary)	620	1240	10	ND	< 4.0
Anesthesiologist (personal)	195	392	10	ND	< 13
Surgeon (personal)	177	353	10	ND	< 14
Left of surgeon (stationary)	260	520	10	ND	< 9.6
Drug administration (stationary)[b]	103	206	10	ND	< 24
Drug suction equipment (stationary)	260	530	10	ND	< 9.4
Anesthesiologist (personal)	92	184	10	ND	< 27
Surgeon (personal)[c]	53	106	10	ND	< 47
Left of surgeon (stationary)	190	380	10	ND	< 13
Drug administration (stationary)	185	370	10	ND	< 14
Drug suction equipment (stationary)	180	360	10	ND	< 14
Blank	–	–	10	ND	

ND, not detected (< 0.5 ng/mL HCl). [a]Stationary sampling about 150 cm above the floor; samples left of surgeon 180 cm above the floor during PIPAC. [b]Sampling intermittent (technical failure). [c]Sampler partly covered by gown; sampling started at administration of the drug.

Table 3: Analysis of gloves and hands of the surgeon for the presence of platinum (PT).

PIPAC	Gloves and hands	Total extraction volume HCl, mL	PT, ng/mL HCl	PT, ng
1	Outer pair of gloves surgeon (white)	100	ND	< 50
1	Inner pair of gloves surgeon (blue)	100	ND	< 50
1	Hands surgeon (3 tissues)	140	ND	< 70
2	Outer pair of gloves surgeon (white)	100	ND	< 50
2	Inner pair of gloves surgeon (blue)	100	ND	< 50
2	Hands surgeon (3 tissues)	140	ND	< 70
Blank	Outer pair of gloves (white)	100	ND	< 50
Blank	Inner pair of gloves (blue)	100	ND	< 50
Blank	3 Tissues	140	ND	< 70

ND, not detected (< 0.5 ng/mL HCl).

Table 4: Analysis of waste line components for the presence of platinum (PT).

PIPAC	Description	Total extraction volume HCl, mL	PT, ng/mL HCl	PT, ng
1	Smoke evacuation filter[a]	30	ND	< 15
1	Infant-pediatric electrostatic filter HME[b]	20	ND	< 10
1	Liquid from water seal drainage	45	ND	< 23
2	Smoke evacuation filter[a]	30	ND	< 15
2	Infant-pediatric electrostatic filter HME[b]	20	ND	< 10
2	Liquid from water seal drainage	43	ND	< 22

ND, not detected (< 0.5 ng/mL HCl). [a]MTP GmbH, Neuhausen Ob Eck, Germany. [b]Medtronic, Brussels, Belgium.

contamination (detection limit < 9 ng/m^3). Recently, Graversen and coworkers reported the results of air sample analysis and biological monitoring in two surgeons during and after PIPAC in two patients [15]. Importantly, the blood analyses were undertaken after 50 PIPAC procedures were performed. No traces of platinum were found in the air samples or in the surgeon's blood. In the present study, we have analyzed contamination of floor surfaces, surgeon's gloves and hand surface, and waste circuit components in addition to air samples. We did not analyze blood samples, since cisplatin is rapidly metabolized and reliable detection of systemic Pt exposure would require serial urinary sample analyses. Our results confirm that, after PIPAC with cisplatin or oxaliplatin, no detectable platinum is present in large volume air samples taken close to the surgeon and anesthesiologist, with a detection limit of 4.0–27 ng/m^3. Moreover, and reassuringly, no platinum was detected in either the filters or in the water contained in the water seal reservoir. This suggests that the electrostatic precipitation at the end of the aerosol delivery ensures complete absorption of the drug by the peritoneal contents.

We were unable to identify platinum contamination of either the inner or the outer pair of surgeon's gloves. In contrast, during HIPEC with open abdomen perfusion and the surgeon's hand stirring the abdominal contents, glove contamination is considerable. Regardless of the procedure, prevention of cutaneous exposure by wearing appropriate gloves is essential. In Europe, there are no specific requirements or test methodologies for medical gloves used for handling cytotoxic agents. In contrast, in the US medical gloves used for this purpose must fulfill the ASTM International (American Society of Testing and Materials) standard D 6978-05 requirements. Nitrile or natural rubber latex are the preferred basic glove materials. Importantly, all glove material displays a general trend towards greater permeation over time (fivefold increase between 15 and 60 min). [22] Therefore, a glove change is recommended every 15–20 minutes, or more frequent with increasing temperature or continuous hand movement.

In conclusion, using the proposed technical setup and precautions, we were unable to detect any surface, air, or material contamination with platinum during or after two clinical PIPAC procedures. These results confirm that, with adequate preparation, a clinical PIPAC program can be established without measurable chemotherapy exposure to health care workers. It is recommended that toxicological analyses are performed before starting a clinical PIPAC program in order to ensure adequacy of the protective measures that are put in place.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: W. Ceelen is a senior clinical researcher from the Fund for Scientific Research – Flanders (FWO).
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Appendix

Before ePIPAC

1. Patient name: …
2. Date: … . … . … .
3. Chemotherapeutic agent(s) ordered? O
4. Laparoscopy pictures taken? O
5. PCI and ascites volume noted? O
6. Biopsies taken at four abdominal quadrants and marked with clips? O

Installation of the ePIPAC injection system

1. Electrode placed and connected to Ultravision System? O
2. Ultravision System turned off? O
3. Patient return electrode placed and connected with electrosurgical generator? O
4. Pneumoperitoneum airtight at 12 mmHg? O
5. Cap applied to balloon port of both trocars? O
6. Port of 5 mm trocar closed? O
7. Filter system connected to 5 mm trocar? Clamp closed? O
8. Filter system connected to water seal drainage system? O
9. Water seal drainage system connected to a wall-mounted suction unit with filter? O
10. Two cm water seal established? O
11. Water seal drainage system in function? O
12. CO_2 tube with filter connected to 12 mm trocar? Port open? O
13. Micropump fixed in 12 mm trocar and end just in the peritoneal cavity? O
14. Is the micropump connected to a high pressure line? O
15. High pressure line and micropump flushed? O
16. Plastic camera cover fixed to the micropump with adhesive strip? O
17. Camera placed in the 5 mm trocar and fixed with laparoscopic camera holder? O
18. Clothing, gloves, instruments and stitches for wound closure present? O

Aspiration of chemotherapy

1.	Does everyone in the room wear safety glasses, gloves and protective clothing?	O
2.	Protective sheet placed under the injector and next to the patient?	O
3.	Chemotherapy waste containers present in the operating room?	O
4.	Chemotherapy, dose and name of patient correctly noted on label?	O
5.	Syringe(s) placed into the pressure injector?	O
6.	Piston of syringe(s) pushed up?	O
7.	Three way stopcock connected to syringe(s)?	O
8.	Chemotherapy bag connected to infusion line?	O
9.	Infusion line connected to 3 way stopcock?	O
10.	After complete aspiration of chemotherapy, syringes vented in chemotherapy bag?	O
11.	After decoupling the 3 way stopcock, high pressure line connected to syringe(s)?	O
12.	Plastic camera cover fixed to syringe(s) with adhesive strip?	O
13.	Syringe volume(s), maximum pressure of 20 bar and flow rate of 30 mL/min set?	O
14.	Laparoscopy screen turned to folding doors?	O
15.	Remote monitoring devices in function?	O
16.	Patient curarized for 40 minutes?	O
17.	Laminar air flow in function?	O
18.	ePIPAC door warning sign placed?	O
19.	All team members leave the operating room.	O

ePIPAC

20.	Remote-controlled administration of chemotherapeutic agent(s).	O
21.	After injection, one person enters the operating room and activates the Ultravision System	O

Completing the procedure

22. After 30 minutes, one person enters the operating room, stops CO_2 insufflation, opens the 5 mm trocar port and opens the clamp of the filter system to safely desufflate the pneumoperitoneum. Removal of electrode of Ultravision System. Wound closure and local anesthesia.
23. The team enters the operating room.
24. Disposable material is collected in chemotherapy waste containers.

References

1. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg 2012;99: 699–705.
2. Thomassen I, Van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. Int J Cancer 2014;134:622–628.
3. Thomassen I, Ve L, Sw N, Luyer MD, Yl K, Ih DH. Incidence, prognosis, and possible treatment strategies of peritoneal carcinomatosis of pancreatic origin: A population-based study. Pancreas 2013;42:72–75.
4. Van Driel W, Sikorska K, Schagen van Leeuwen J, Schreuder H, Hermans R, de Hingh I et al. A phase 3 trial of hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer. J Clin Oncol 2017;35(suppl; abstr 5519).
5. Dehal A, Smith JJ, Nash GM. Cytoreductive surgery and intraperitoneal chemotherapy: An evidence-based review-past, present and future. J Gastrointest Oncol 2016;7: 143–157.
6. Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010–2015. Syst Rev Crit Rev Oncol Hematol 2016;100:209–222.
7. Wu Z, Li Z, Ji J. Morbidity and mortality of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in advanced gastric cancer. Transl Gastroenterol Hepatol 2016;1:63.
8. 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: 1849–1855.
9. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: A cohort study. Anticancer Res 2015;35:6723–6729.
10. Demtroder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis 2016;18:364–371.
11. Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hubner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. Br J Surg 2017;104: 669–678.
12. Kakchekeeva T, Demtroder C, Herath NI, Griffiths D, Torkington J, Solass W et al. In vivo feasibility of electrostatic precipitation as an adjunct to pressurized intraperitoneal aerosol chemotherapy (ePIPAC). Ann Surg Oncol 2016;23:592–598.
13. Reymond M, Demtroeder C, Solass W, Winnekendonk G, Tempfer C. Electrostatic precipitation pressurized

intraperitoneal aerosol chemotherapy (ePIPAC): First in-human application. Pleura and Peritoneum 2016;1:109–116.
14. Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): Occupational health and safety aspects. Ann Surg Oncol 2013;20:3504–3511.
15. Graversen M, Pedersen PB, Mortensen MB. Environmental safety during the administration of pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pleura and Peritoneum 2016;1:203–208.
16. Kyriazanos I, Kalles V, Stefanopoulos A, Spiliotis J, Mohamed F. Operating personnel safety during the administration of hyperthermic intraperitoneal chemotherapy (HIPEC). Surg Oncol 2016;25:308–314.
17. Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. A review of human carcinogens–Part A: Pharmaceuticals. Lancet Oncol 2009;10:13–14.
18. Villarini M, Gianfredi V, Levorato S, Vannini S, Salvatori T, Moretti M. Occupational exposure to cytostatic/antineoplastic drugs and cytogenetic damage measured using the lymphocyte cytokinesis-block micronucleus assay: A systematic review of the literature and meta-analysis. Mutat Res 2016;770:35–45.
19. Villa AF, El Balkhi S, Aboura R, Sageot H, Hasni-Pichard H, Pocard M, et al. Evaluation of oxaliplatin exposure of healthcare workers during heated intraperitoneal perioperative chemotherapy (HIPEC). Ind Health 2015;53:28–37.
20. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf [last accessed May 27, 2017].
21. Landeck L, Gonzalez E, Koch OM. Handling chemotherapy drugs-Do medical gloves really protect? Int J Cancer 2015;137:1800–1805.