

Chapter

PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC): OCCUPATIONAL HEALTH AND SAFETY MANAGEMENT

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ABSTRACT

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is an innovative drug delivery system applying chemotherapy as a pressurized therapeutic aerosol into the abdominal cavity. PIPAC has superior pharmacological properties and first clinical results concerning efficacy and safety are promising. However, applying chemotherapeutic substances as a toxic aerosol is a challenge for occupational health and safety management. A risk assessment of PIPAC was performed to meet legal requirements. It was not possible to replace chemotherapeutic drugs with other substances since platin-based drugs and/or anthracyclines are the drugs of choice in many peritoneal cancers. However the dose of toxic substances could be reduced by 90%. Exposure of health workers to the chemotherapeutic drugs can be cutaneous (liquids) or respiratory (aerosol). Wearing chemotherapy gloves, protective clothing and glasses was effective for preventing cutaneous or ocular exposure, since the drugs applied are not absorbed through the skin. A three-level confinement system was designed to prevent any inhalative exposure of health workers. The first level is the closed abdomen itself, which tightness is controlled before chemotherapy application. The second level is the volume

of the operating room together with air exchange through high-flow ventilation. The third confinement is the physical operating room, since the PIPAC procedure is remote-controlled and the team leaves the room during application. At the end of the procedure, the toxic aerosol is exhausted through a Closed Aerosol Waste System (CAWS) over a special line into the external environment, using the same system used for eliminating narcosis gases. Repeated environmental measurements in two different hospitals according to NIOSH protocols at the potential working places of the surgeon and of the anesthesiologist detected no traces of platin in the air. Biological monitoring in the blood of 5 surgeons after 500 procedures showed no traces of platin or doxorubicin. Mathematic modelling of the worst case scenario (immediate release of the toxic aerosol into the working environment) showed a potential respiratory uptake lower than 1/100'000 of a usual systemic chemotherapy dose. Over 650 procedures, to minor incidents related to disconnection in the tubing system were reported in the Critical Incident Reporting System (CIRS). No severe incident, in particular no leakage of the toxic aerosol, was recorded. No pressure- or technology-linked patient complication was noted. Work place measurements remained below the tolerance margin. The safety measures and conditions as defined above are sufficient. PIPAC can be used safely in the clinical setting if the conditions specified above are met. For the drugs tested, PIPAC is in compliance with European Community working safety law and regulations.

INTRODUCTION

Local drug administration has been used as a therapeutic modality for many years and for a broad spectrum of indications. Drugs can be delivered locally as powder (e.g. talcum into the pleural space), as a liquid (e.g. intraperitoneal chemotherapy) or as an aerosol (e.g. nasal spray). Among these possibilities, delivering drugs as an aerosol has significant benefits, including ease of use, patient comfort, dose reduction, greater selectivity, and the potential to decrease side effects [1].

As a consequence, aerosol formulations have found wide application, in particular in pulmonary medicine for treating asthma, chronic obstructive lung disease, allergies, etc. A further indication for aerosols in pulmonary medicine is lung cancer [2]. Several chemotherapeutic agents have been tested in this indication in vitro or in vivo (reviewed in 3).

Recent phase I studies have demonstrated the feasibility and safety of aerosol delivery of doxorubicin [4] and gemcitabine [5] in lung cancer patients. In the abdomen, the use of intraperitoneal drug delivery in the treatment of malignant disease confined to the peritoneal cavity is based on the potential for increased exposure of the tumor to antineoplastic agents leading to improved cytotoxicity.

In patients with tumors confined to the peritoneal cavity, there is established pharmacokinetic and tumor biology-related evidence that intraperitoneal drug administration is advantageous. Clearly, intraperitoneal drug delivery is an important adjunct to surgery and systemic chemotherapy in selected patients [6]. However, there are practical and theoretical concerns about intraperitoneal chemotherapy with liquids including [7]:

1. Adequacy of drug distribution throughout the entire peritoneal cavity
2. Limited direct penetration of drugs into tumor or normal tissue
3. Decrease in the delivery of drug to the tumor by capillary flow (through the systemic circulation) after regional delivery

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4. Unique toxic effects associated with local delivery—eg, abdominal pain, bowel perforation, infection, and obstruction
5. Added time, inconvenience, and cost associated with the specific requirements of regional delivery—eg, catheter placement

These concerns explain why, despite the positive effect of intraperitoneal chemotherapy on progression-free and overall survival in selected patients with small volume peritoneal carcinomatosis, this management strategy is not broadly accepted and finds only limited use in clinical practice.

PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC)

A new way of intraperitoneal chemotherapy is the application of cytotoxics in form of a pressurized aerosol into the abdominal cavity. We first described the principle of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) 15 years ago [8]. PIPAC relies on logical physical principles: local administration into the body cavity to improve therapeutic ratio, gaseous form to achieve homogeneous drug distribution, pressure application to enhance convective drug uptake into tumor nodes, and minimally-invasive approach to minimize operative trauma. PIPAC allows repeated therapy cycles and objective tumor response assessment (reviewed in 9). PIPAC has superior pharmacological properties and first clinical results concerning efficacy and safety are promising [10].

PIPAC technology (Figure 1) uses a laparoscopic access via ports through the abdominal wall. In a first step, a normothermic (37 °C) capnoperitoneum (CO₂) is established with a pressure of 12 mmHg. Using a specific high-pressure injector and a micropump, a cytotoxic solution is aerosolized into the abdominal cavity, and maintained for 30 min.

At the end of the procedure, the aerosol is removed through a closed suction system. Since its physical behaviour is similar to an ideal gas, an aerosol applied in the peritoneal cavity allows a homogeneous distribution of the chemotherapeutic agent within the closed abdominal space [11]. Furthermore, an artificial pressure gradient is generated that overcomes tumoral interstitial fluid pressure and results in higher tissue drug penetration compared to conventional intraperitoneal or intravenous chemotherapy [12-14]. At the same time the plasma concentration of the chemotherapeutic agent remains low [15]. However, delivering chemotherapy as an aerosol is a challenge for occupational health and safety management because it carries a potential risk of accidental exposure of health care workers as compared with other administration routes. This is due to the difficulty to control the spread of aerosols which in turn contributes to the risk of unwanted exposition. This problem is not new and technical solutions have already been proposed. For example, in pulmonary medicine, a tent system combined with HEPA filters has been proposed to reduce this risk to a minimum during aerosol chemotherapy.

This system was shown to be effective at containing any nebulized liposomal encapsulated cisplatin during patient treatment [16]. A similar challenge is raised by PIPAC. To prevent any harm to health care workers, we have identified and evaluated potential hazards concerning occupational exposures during PIPAC performance.

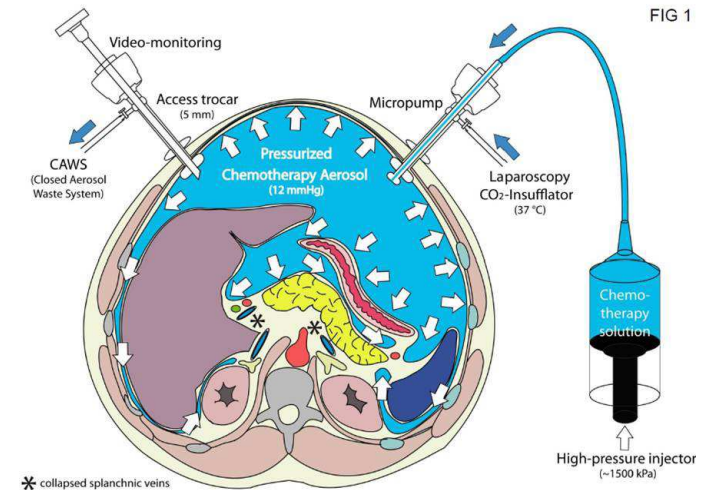


Figure 1. Technique of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC).

A capnoperitoneum of 12 mmHg is established as usual during laparoscopy. A chemotherapy aerosol is generated at the tip of a mechanical micropump introduced through a balloon trocar, and maintained for 30 min at 37°C. Then, the toxic aerosol is exsufflated over a secure system (CAWS: Closed Aerosol Waste System) into the outside environment.

In a second set of experiments, we have simulated PIPAC in the laboratory and in the operating room. Then, we have applied PIPAC in the human patient using chemotherapeutic drugs and measured contamination levels under real clinical conditions.

Later on, we have sampled body fluids, looking for the presence of traces of chemotherapy in healthcare workers. Finally, we have simulated accidental exposure by developing mathematical models in the worst case scenario.

METHODS

Ethical, Legal and Regulatory Background

The study protocol was submitted to the Institutional Review Board (IRB, Common Ethics Committee of the Westfalian Wilhelms-University Münster and of the Westfalian Medical Chamber).

The IRB recommended performing the first PIPAC therapy with volunteers, which were extensively informed and trained in the PIPAC procedure. PIPAC application was performed within the framework of regulatory studies (PIPAC-OV1; PIPAC-GA1; PIPAC-OV2) and as off-label use according to German Drug Act (AMG).

Methodology

The following steps were defined: identification of hazardous substances and dose; identification of possible exposure ways; simulation of the PIPAC procedure with non-toxic aerosols and smoke; redaction of Standard Operating Procedures (SOP); 2nd simulation according to the SOP; informing and training of the health care workers; performance of the first two PIPAC procedures with chemotherapeutic substances and workplace measurements under real conditions.

These steps were determined together with an external company specialized in occupational health safety in the chemical industry (DEKRA Industrials, Stuttgart, Germany). After successful workup in the first institution (Evangelic Hospital Bielefeld, Germany), we repeated the measurements in a second hospital (Marien Hospital Herne, Ruhr-University Bochum, Germany) under supervision of a second independent company (Dräger Safety, Lübeck, Germany).

After 500 PIPAC procedures, blood samples were taken from the 5 surgeons and gynaecologists having performed these procedures. Incidents were recorded prospectively with a Critical Incident Reporting System (CIRS).

Finally, mathematical simulation allowed to determine theoretical contamination levels in the worst case scenario (complete release of the toxic aerosol into the working environment).

Aerosolizer

The micropump (MIP®, Reger Medizintechnik, Rottweil, Germany) has been described elsewhere [17]. In brief, it consists of several components, including a shaft and a nozzle. The nozzle has a diameter of 0.2 mm. A pressure of up to 20 bar is delivered through a high-pressure line upstream of the micropump, using an industry-standard injector for vascular surgery (Mark 7 Arterion, Bayer Healthcare, Berlin, Germany), including a remote control device.

Operating Room Characteristics

PIPAC procedure was performed within an operating room (OR) equipped with laminar air flow. Volume of the OR was approximately 168 m³. Air flow was 1.8 x 10⁶ L/h. Room temperature was 22.3-22.6 °C. Relative humidity was 36-37%. Atmospheric pressure was 994 hPa. Vacuum was generated with a negative pressure of -0.85 bar (Dräger, Lübeck, Germany).

Chemotherapy

We have focused on the application of two chemotherapeutic agents: cisplatin and doxorubicin. Chemotherapy was applied as following: nebulization over 3-6 minutes of 7,5 mg cisplatin/m² body surface followed immediately by the aerosolization of 1,5 mg

doxorubicin/m² body surface into the abdominal cavity filled with CO₂ at a pressure of 16 to 20 mbar (12 to 15 mmHg) at a temperature of 37°C followed by 30 min steady-state before exsufflation.

Experimental Protocol

PIPAC procedures were performed in peritoneal cancer patients. Between the procedures, the room was cleaned according to the hospital's standard hygiene and surface cleaning protocols.

Each procedure was structured into 4 consecutive phases:

- **Phase 1:** CO₂ insufflation over an industry-standard trocar (Kii Access System, Applied Medical, Darmstadt, Germany), with a target pressure of 16 mbar (12 mmHg). The access system was secured with an intra-abdominal balloon and an extra-abdominal obturator, ensuring tightness of the abdomen and steadiness of the pressure. Two 5- mm working trocars are inserted.
- **Phase 2:** Introduction of a micropump (MIP®, Reger Medizintechnik, Rottweil, Germany) through the access trocar and aerosol formation of the chemotherapy solution into the abdominal cavity using the high pressure injector.
- **Phase 3:** The system was kept in steady-state for 30 minutes at a constant pressure and temperature. The abdomen is hermetically sealed and the total gas flow is minimal.
- **Phase 4:** At the end of the procedure, the gas from the abdomen was released directly into the hospital's air waste system over one of the trocars and an aerosol/smoke filter (pores 0.027 µm, model 03110-10, MTP, Neuhausen ob Eck, Germany).

MATHEMATICAL SIMULATIONS

Modelisation was performed with MatLab® software (MathWorks, Natick, MA, USA).

Risk Assessment

Risk assessment was performed beforehand, before first PIPAC application in the human patient. Following steps were taken:

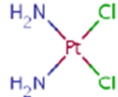
Identification of Hazardous Substances and Dose

For PIPAC, drug choice was derived from the protocol of the German Society for General and Visceral Surgery (DGAV) for CytoReductive Surgery (CRS) and Hyperthermic IntraPeritoneal Chemotherapy (HIPEC) [18].

Cisplatin

Cisplatin is highly poisonous. It can provoke anaphylactic reactions; irritates eyes and skin, has no transdermal absorption. Cisplatin irritates airways, has a cumulative toxic effect on kidney, bone marrow and the inner ear. It is probably carcinogenic to humans. Cisplatin toxicological characteristics are summarized in Table 1.

Table 1. Toxicological characteristics of cisplatin

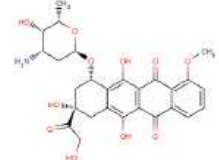
Parameter	Value
CAS-/EG Number	15663-27-1 / 239-733-8
Formula	
Molecular weight	300.06 g/mol
Melting point	270°C; dark yellow powder at room temperature
Boiling point	Not applicable
Steam pressure	Not applicable
Water solubility	2.530 g/L [25°C]
LD50 oral	20 mg/kg (rat) 32 mg/kg (mouse)
NOAEL ¹	No data
Important toxicological details	Acute toxicity: very toxic Skin and eye irritation No evidence for transdermal absorption Cumulative damage of kidney, bone marrow and inner ear No evidence for carcinogenicity in human Evidence for carcinogenicity and teratogenicity in mouse and rat Level of carcinogenicity: 2A Anaphylactic reactions reported Sensibilisation of skin and airways
Total amount of applied cisplatin	15 mg in 150 ml NaCl 0.9 %
Concentration of applied solution	0.1 mg/ml=0.1 g/L=0.01 %
Total applied amount of cisplatin	150 ml
Workplace exposure limits	Germany: not available Netherlands: 0.00005 mg/m ³

Doxorubicin

Doxorubicin is hazardous to human health by provoking mucosal inflammation, leucopenia as well as dilative cardiomyopathy. Additionally, it induces DNA mutation and is carcinogenic to humans. Doxorubicin toxicological characteristics are summarized in Table 2.

The total dose applied during PIPAC (s. above) is approximately 10% of a usual systemic chemotherapy dose. There is no legal exposure limit for either of these two substances in Germany. However, in the Netherlands, the maximally allowed air concentration for cisplatin is <0.00005 mg/m³.

Table 2. Toxicological characteristics of doxorubicin

Parameter	Value
CAS-/EG Number	23214-92-8 / 245-495-6 25316-40-9 / 246-818-3 (Hydrochloride)
Formula	
Molecular weight	543.52 g/mol
Melting point	205°C (Degradation); crystallized powder at room temperature
Boiling point	Not applicable
Steam pressure	Not applicable
Water solubility	0.0928 g/L [25°C]
LD50 oral	570 mg/kg (mouse)
NOAEL1	No data
Important toxicological details	Acute toxicity: harmful Dilatative cardiomyopathy Inflammation of mucosa Leucopenia Evidence for carcinogenicity in animals Evidence for mutagenicity in animals Level of carcinogenicity 2A
Total amount of applied doxorubicine	3 mg in 150 ml NaCl 0.9 % solution
Concentration of applied solution	0.02 mg/ml=0.02 g/L=0.002 %
Total applied amount of doxorubicine	150 ml
Legal upper limit for working place	Germany no upper legal limit

Identification of Possible Exposure Ways

Identified exposure ways are ocular, dermal and inhalative exposition. Other possibilities were reasonably excluded. The preparation of the chemotherapeutic agents in the hospital pharmacy and their transport in adequate containers to the operating room is organized according to the German guidelines [19]. The hospital pharmacy is certified. Both agents are provided in a closed delivery system (special injection syringes filled with NaCl 0.9% solution) in a double envelope, together with patient identification tags and labels defining agent and dose. The syringes are hermetically sealed with special caps.

SIMULATIONS**First PIPAC Simulation with Physiological Solution Aerosols**

Before performing the first clinical PIPAC application, the procedure was simulated in the operating room using a laparoscopy training phantom and non-toxic NaCl 0.9% aerosol.

Working steps were identified and a first operating protocol written. Based on this protocol, risk analysis was performed within an interdisciplinary team including physicians (surgeons and anaesthesiologists), scrub nurses, hospital technicians, the engineers having developed the PIPAC technology and occupational health experts in order to list a maximal number of safety issues, from a 360° perspective. A chronological protocol of the procedure was designed. Possible failures were defined at each step of the procedure, related to the personnel, the patient, the high-pressure injector, the infusion line, the CO₂ insufflator, the access trocars, the micropump itself, the laminar air flow system, the tightness of the abdomen and the exhaustion of the aerosol. For each issue identified, the expected frequency and severity were determined. Then, appropriate safety measures were defined step by step. On this basis, a standard operating protocol was established that served as the basis for the second simulation.

Second PIPAC Simulation with Smoke and an Artificial Leak

The second simulation was performed in the operating room under strict implementation of the standard operating procedures. The abdomen was simulated with a sealed plastic container of similar dimensions. An aerosol of CO₂ and smoke with the same pressure as during laparoscopy (12 mmHg) was installed and industry-standard technical instruments (access trocars, video camera, grasping forceps) were tested. We decided to choose double-balloon access trocars (Kii access port, Applied Medical, Düsseldorf, Germany) to guarantee complete tightness of the abdomen. We excluded CO₂ insufflators equipped with a recapture function in case of overpressure, in order to prevent any release of chemotherapy-loaded CO₂.

We were able to perform the complete procedure without any incident; in particular, the system remained tight. Then, a maximal leakage was simulated (an access trocar was fully opened). The smoke escaping from the leak was flowing downward to the floor and into the lateral outflow windows of at floor level of the operating room (Figure 2).

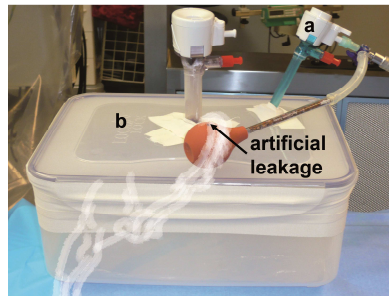


Figure 2. PIPAC simulation with smoke and artificial leakage: sealing access trocars (a) were introduced into a sealed plastic box (b) with the same volume dimensions as the human abdominal cavity. The box was pressurized with CO₂ and steam. Via an artificial leakage (open access trocar), the steam (white bold arrows) was observed to be directed to the floor and not randomly distributed within the operating room. This is caused by the laminar air flowing downwards from the ceiling to the floor.

DESIGN OF A SAFETY CONCEPT

Based on the experience from both simulations, and together with the consulting engineers, we then designed a comprehensive safety concept taking into account all possible incidents and their prevention.

Safety Concept for Cutaneous Exposition

Cutaneous absorption of anthracyclines (such as doxorubicine) and platin-based chemotherapeutics has not been documented. However, local skin contact with chemotherapy solutions might lead to cutaneous irritation or even chemical burns.

Since PIPAC is applied within a closed system, the risk of skin contamination with chemotherapy is minimal. Under normal working conditions, a skin contact with chemotherapy is excluded. For such a contact to occur, a human or material failure has to be assumed, e.g. due to a manipulation error with the high pressure injector, or use of inadequate, low-pressure infusion tubing leading to explosion of the system, wrong line connections, etc.).

During PIPAC preparation, application and termination, the potential risk of skin contamination with chemotherapy solutions can be adequately met by wearing protective, water-proof surgical clothing and special chemotherapy gloves.

The risk of ocular lesions (keratitis, inflammation of the anterior eye chamber, scar formation, etc.) is satisfyingly met by wearing protecting glasses or transparent masks covering the entire face. This risk can be further reduced by providing sterile one-block systems (nebulizer and infusion tubing sealed together with secured, doubled connections), and by training and drilling the team in order to minimize human errors.

The floor of the operating room under the high-pressure injector and the connecting line is covered by a waterproof protection sheet. Commercial sets are available in order to remove chemotherapy solution in case of spillage, and are available in the OR.

The operating room has to be cleaned after each PIPAC procedure – as a standardized procedure by trained personnel. Tissues, tubes, lines and other devices such as operation drapes and sponges have to be disposed into special, sealed chemotherapy waste containers with adequate labelling.

Safety Concept for Respiratory Exposition

A safety concept consisting of three consecutive levels of confinement was designed in order to prevent any accidental respiratory exposition of the personnel to the chemotherapy aerosol. These 3 levels of confinement are (Figure 3):

- The closed abdomen
- The operating room and the ventilation system
- Remote-controlling of the procedure.

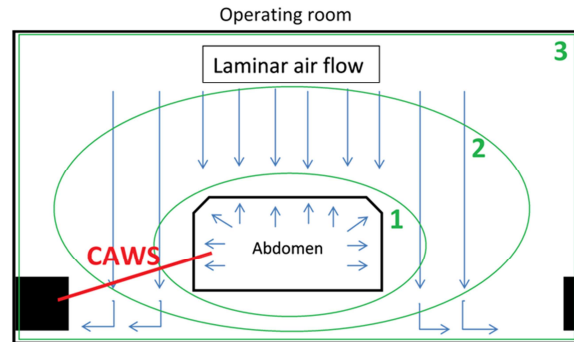


Figure 3. A safety concept consisting of three consecutive levels of confinement was designed in order to prevent any accidental respiratory exposition of the personnel to the chemotherapy aerosol. These 3 levels of confinement are: The closed abdomen, The operating room and the ventilation system and Remote-controlling of the procedure. At the end of the PIPAC procedure, a single person enters the operating room and opens the gas evacuation system (Closed Aerosol Waste System, CAWS) designed to discard the toxic aerosol without risk of exposition.

The tightness of the abdomen can be easily controlled by a zero-flux from the CO_2 insufflator. However, CO_2 is absorbed by the organism so that a flow rate of 0.1 L/min (max 0.2 L/min) is acceptable.

The second confinement level is more complex and consists of the operating room and the ventilation system together. A usual operating room has a volume between 120 and 150 m^3 so that a leakage of few litres CO_2 would be significantly diluted (by a factor of about 50'000). Modern operating rooms are equipped with high-flow ventilation systems ensuring rapid air exchange. The pre-treated air can be cooled, warmed and/or humidified according to the need. Then, it is filtered through one or several series of filters placed in the ventilation tubing (in the rule so-called F-filters) and/or in the ceiling of the operating room (so-called H-filters). In some cases, a ventilator ensures a continuous air flow from the operating room ceiling in cases of pressure loss in the ventilation system. The air enters the operating room through a micro-perforated ceiling (ventilation) or through advanced systems generating a laminar air low (without turbulences). Aspiration of the air is provided through caption exits at the floor level, with anti-reflux valves generally equipped with pressure-regulating feed-back systems.

The principle of a typical ventilation system is described in Figure 4.

The detailed description of the various filters and corresponding ISO norm 14644 goes beyond the scope of this work but is available in the specialized literature [20]. Some ventilation systems can be programmed to function with negative pressure aspiration, which is advantageous for performing PIPAC because any air contamination of independent rooms can be completely excluded. The third level of confinement consists of the walls of the operating room, since the procedure is remote-controlled and the personnel is leaving the operating room just before application of the chemotherapeutic aerosol.

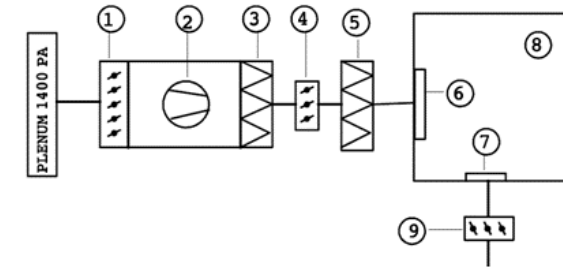


Figure 4. Example of a typical air-filtering system in the operating room. The air enters the system through a motorized valve system (1), is propelled by a ventilator (2) through the first series of filters (e.g. F9 filters). Then, the air goes through a motorized disinfection valve system and a second series of filters (e.g. H12 filters) before entering the operating room (8) through a perforated ceiling (6). The air is aspirated through the exit openings (7) at the floor level and discarded through an anti-reflux valve system (9).

In case of emergency, it is possible for a surgeon or for an anaesthesiologist to enter the operating room for delivering drugs, etc. However, the presence time in the area at risk should be kept as short as possible. At the end of the PIPAC procedure, a single person enters the operating room and opens the gas evacuation system (Closed Aerosol Waste System, CAWS) designed exclusively to discard the toxic aerosol without risk of exposition (this is not the usual suction system used by surgeons in the operating room).

The CAWS consists of a closed line connecting the valve of a single access trocar with the wall suction plug routinely used by the anaesthesiologists to evacuate narcosis gases. Two micro-particle filters are placed in series to further limit the risk of contamination of the working environment with chemotherapy micro droplets. During the PIPAC procedure, the CAWS is closed by two valves in order to exclude any premature exsufflation of the abdomen.

INFORMATION AND TRAINING

On the basis of the successful simulations, it was decided to schedule two patients for the first PIPAC procedures. Information meetings allowing open, interactive discussion were organized since the planned procedures had raised emotional concerns, in particular among scrubbing nurses and cleaning workers.

On the basis of these discussions, we decided to restrict the first procedure to volunteers within the framework of a special shift under exclusion of other simultaneous surgical procedures. Before the first procedure, the team of volunteers received interdisciplinary training according to the standard operating procedures. Access to the operating room where PIPAC is applied was strictly restricted, the area was signalled with warning shields on each access door. These shields were turned on the backside at the end of the procedure.

SAFETY ASSESSMENT

In occupational settings, environmental monitoring of exposure to toxic aerosols seems to be superior to biological monitoring. It offers the possibility of simultaneous determination of components of mixtures, is simple to interpret, and evaluates short-term exposure to environmental irritants [21]. Thus, estimation of exposure under real conditions was an important step to provide a safe working environment during PIPAC.

First Environmental Assessment

The two first PIPAC procedures worldwide were performed on Nov. 5th, 2011 at the Evangelic Hospital in Bielefeld, Germany. The operating setting is shown in Figure 5.

The standard operating protocols were strictly implemented; in particular, nobody remained within the operating room during the PIPAC procedure, which was remote-controlled. The nebulizer functioned as expected and the system remained air tight. At the end of the procedure, the chemotherapy aerosol was exhausted into the air waste system of the hospital and released into the outside environment.

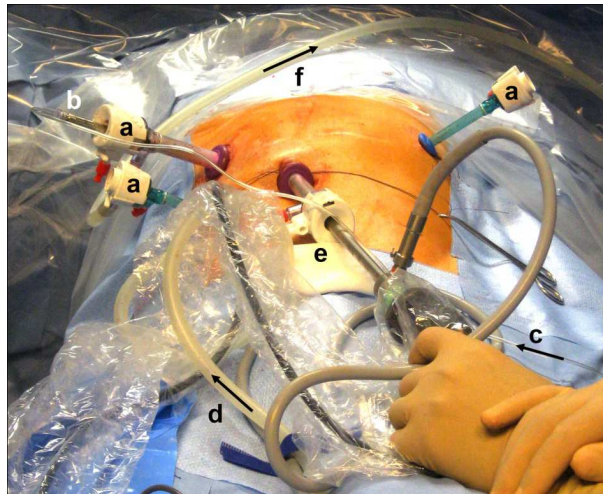


Figure 5. First PIPAC under real conditions: Access trocars (a) with the nebulizer (b) in situ. The chemotherapeutic agents were transported from the injector to the nebulizer via a high-pressure infusion line (c). CO₂ was injected into the abdominal cavity via a standard gas line (d) and the trocar (e); (camera trocar). At the end of the procedure, the chemotherapeutic capnoperitoneum was exsufflated via closed line (f) over two serial microparticle filters into the air waste system of the hospital. Dark arrows indicate the flow direction of the gas and chemotherapeutics, respectively.

* = trocar sealing rings.



Figure 6. Operating room (OR) set up for first PIPAC and safety measurement. The OR is equipped with laminar air-flow. The abdomen is tight. The procedure is remote-controlled. Environmental air sampling was undertaken at the surgeon's (a) and anesthesiologist's (b) working positions. The pressure injector (c), sealing trocars and nebulizer in situ (d) and also the exsufflation line (e) are shown. To minimize any possible chemotherapeutic exposure of the anesthesiology crew, a transparent curtain dividing the laminar air flow was hung vertically 50 cm above the access trocars, between the patient's head (position of the physician) and the abdomen (site of chemotherapy application).

The procedure was scheduled on a holiday and no other surgical procedure was performed at that time in any other room. The procedure was performed under the supervision of a safety officer and included workplace air measurements. Air was sampled during two consecutive PIPAC procedures. The operating room setting including safety measures and air sampling devices at the putative positions of the surgeon and of the anaesthesiologist are shown in Figure 6.

The probe sampling system used was a Gravikon VC25 device combined with a dust detector (Ströhlein, Kaarst, Germany). Air was collected on a cellulose nitrate filter with a diameter of 50 mm, with a flow of 22.5 m³/h. Toxicological research analysis of cisplatin levels was performed according to a standard protocol (NIOSH 7300). The detection limit was 0.3 µg/sample. Sampling and analysis were performed by engineers of the Division for Hazardous Substances at the Laboratory for Environmental and Product Analysis of DEKRA Industrial GmbH in Stuttgart (Germany), an independent certification organization. Results are summarized in Table 3. Air analysis showed no traces of cisplatin, neither at the position of the surgeon nor at the position of the anaesthesiologist [22].

Table 3. Measurement of platinum concentration in the operating room

Measurement points	1	2
Probe N°	0511-01	0511-02
Date	05.11.2011	05.11.2011
Start [hh:mm]	12:15	12:15
End [hh:mm]	16:38	16:38
Duration [h]	2.4	2.4
Airpressure [hPa]	994	994
Temperature [°C]	22.5	22.5
Volume stream [m ³ /h]	22.5	22.5
Partial gas volume [m ³]	54.2	54.0
Platinum in inhalable dust [mg/Pr.]	0.3	0.3
Limit of Determination (LoD) [mg/Pr.]	0.3	0.3
Relative LoD [mg/m ³]	0.000006	0.000006
Analysis [mg/Pr.]	< 0.3	< 0.3
Concentration [mg/m ³]	< 0.000006	< 0.000006
Platinum calculated as cisplatin		
Concentration [mg/m ³]	< 0.000009	< 0.000009

Nota :

(a) To allow a precise analysis of the limit of determination (LoD), probe sampling was performed during two operations but only when chemotherapeutic drugs were applied. In the meantime, sampling was paused. (b) Measurement locations:

¹ Anaesthesiologist's position- patient head, 150 cm above floor.

² Surgeon's position – patient abdomen, 150 cm above floor.

Second Environmental Assessment

A second set of environmental measurements was commissioned when PIPAC procedures were started in a second hospital (Marien Hospital Herne, Ruhr University Bochum, Germany). Evaluation was performed by Dräger Analytical, Lübeck, Germany in order to exclude a potential release of hazardous substances into the air during PIPAC therapy. Again, platinum concentration was used as a tracer for possible contamination of the circulating air. For the second assessment, another probe sampling system was used, consisting of a Gravikon PM 4.2 device combined with a dust detector (Ströhlein, Kaarst, Germany). Air was collected on a cellulose nitrate filter with a diameter of 50 mm, with a flow of 4 m³/h. The absolute detection limit for platinum was 0.0005 mg, corresponding to 0.00013 mg/m³ for 4m³ air. Blinded analysis of the test and control samples was performed by Kiwa Control GmbH, Rostock, Germany, by flameless atomic absorption spectrometry (AAS), executed with inductive coupled plasma (ICP-OES).

All probes remained negative, meaning that no traces of platinum could be detected in the air. Thus, this second assessment confirmed the absence of air contamination during PIPAC in a second institution with different technical setup in the operating room [23].

BIOLOGICAL MONITORING

In Germany, biomonitoring is required by law in the context of occupational health as a secondary prevention measure for the identification of individual load after exposure to hazardous substances. For many hazardous materials, including many chemotherapeutic drugs, the individually recorded load is quantifiable by biomonitoring and thus assessable. The aim of biomonitoring is to take appropriate measures (improvement of technical, organizational and personal prevention) to reduce the burden and the health hazard (reviewed in 24).

In particular, biomonitoring should be taken into consideration in activities (non-exhaustive list):

- where direct skin contact with hazardous substances is possible,
- for which exposure to hazardous substances with long biological half-life is present,
- when exposed to carcinogenic or mutagenic substances,
- when exposed to mutagenic substances,
- where the hazardous substances are difficult to measure in the air,
- in case of accidental exposition to hazardous substances.

Some of these conditions are clearly given for health workers administering PIPAC to patients. Therefore, after 500 PIPAC procedures, blood was sampled from all 5 surgeons and gynecologists performing PIPAC on a regular basis in our institution. Samples were taken by an independent physician. Serum concentrations of doxorubicin and cisplatin were determined by an independent laboratory. After obtaining consent of the physicians examined, we could collect all individual results: all samples remained negative, meaning that no traces of cisplatin or doxorubicin could be detected in the persons with the highest risk of potential exposure to toxic aerosols (data on file). Thus, the probability that other health workers have been exposed is extremely low, since no one of these individuals applied PIPAC in patients.

MATHEMATICAL MODELIZATION, WORST CASE SCENARIO

A further step in PIPAC risk assessment is to evaluate the worst case scenario, namely the case of complete release of the toxic aerosol into the working environment, in order to be able to determine the degree of exposition of the crew in such an extreme case. For this purpose, we performed mathematical simulations. The assumptions made on the basis of physiological, clinical and technical data available are given in Table 4. In addition, it was assumed that the aerosol behaves like an ideal gas, meaning that it is homogeneously distributed within the volume of the operating room after release. Finally, it was assumed that the volume of the abdomen remains constant because leakage is compensated by the CO₂ insufflator.

For calculating what would happen in the case of complete aerosol release, we first determined both extreme boundary scenarios (limits):

- all-at-once release of the aerosol (immediate, complete release at the beginning of PIPAC application)
- continuous release of the whole aerosol over time (slow release until completion of the procedure).

By definition, any leakage mode will lie between these both limits so that the real exposition can be assumed to lie between the boundaries calculated for these scenarios.

IMMEDIATE RELEASE SCENARIO

The first scenario presupposes an all-at-once release of the whole toxic aerosol immediately after application. Mathematically this scenario can be described by an exponential function. The following function describes the trend of the concentration of the chemotherapeutics in the operating room depending on the time.

$$c_1(t) = c(t_0) * e^{-a*t} \text{ with } c(t_0) = \frac{m_{start}}{V_{OR}}$$

where $c_1(t)$ = concentration over time, t_0 = concentration at time 0, m_{start} the administered dose of chemotherapeutics, V_{OR} the volume of the operating room, and a the air exchange rate through the laminar flow.

SLOW RELEASE SCENARIO

The second scenario describes the slow, continuous release of the whole aerosol over a period of 30 minutes. This scenario can also be described by a composition of exponential functions.

$$c_2(t) = c(t_0) * (1 - e^{-b*t}) * e^{-a*t} \text{ with } c(t_0) = \frac{m_{start}}{V_{OR}}$$

where b is the rate of toxic agent leaving the abdominal cavity over time.

The curves for both scenarios are shown in Figure 7. Differences between both boundary scenarios are obvious. The immediate release scenario results in a about 50 times higher peak concentration of chemotherapeutic substances in the air of the operating room than the slow release scenario. Moreover, the timepoint of the maximal potential exposition is different, immediate in the first scenario and after about 3 minutes in the second scenario. In both scenarios, the concentration of toxic substances in the air can be considered to be insignificant after 12 to 15 minutes operating time.

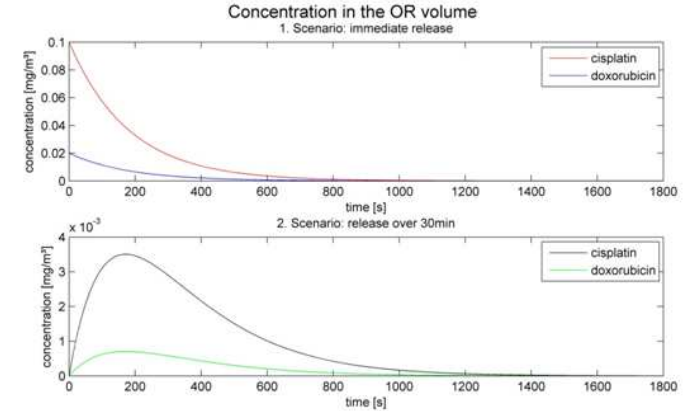


Figure 7. Concentration over time of cisplatin and doxorubicin in the air of the operating room (OR) after total leakage during PIPAC. Upper panel: immediate release scenario. Black curve: cisplatin; blue curve: doxorubicin. Lower panel: slow release scenario. Black curve: cisplatin; green curve: doxorubicin. The y-axis scale differs between panels by 3 orders of magnitude.

Table 4. Assumptions made for mathematical modelization of the worst case scenario (complete release of the toxic aerosol into the working environment)

Parameter	Value
Volume of the operating room	150 m ³
Volume of the abdomen	3 liters
Body surface	2 m ²
Application time	30 minutes
Air exchange rate	50 m ³ /min
Breathing volume	5 liters/min
Administered doses:	
Cisplatin	15 mg
Doxorubicin	3 mg

Inhaled Dose

In a second step, to determine the inhaled dose, it is necessary to multiply the concentration with the minute breathing volume.

Then, an integer function supplies the dose inhaled over time. To get the integration constant it is necessary to know the context.

For the first scenario (immediate complete release), following function applies:

$$d_1(t) = \int_0^t c_1(\tilde{t}) * \dot{V}_{breathed} d\tilde{t} + \text{const}$$

Obviously it must be: $d_1(t=0) \stackrel{!}{=} 0 \Rightarrow \text{const} = \frac{c(t_0) * \dot{V}_{breathed}}{a}$

$$\Leftrightarrow d_1(t) = c(t_0) * \dot{V}_{breathed} * \frac{1}{a} * (1 - e^{-a*t})$$

where $\dot{V}_{breathed}$ is the volume breathed/minute. In analogy, the same steps are necessary to calculate the inhaled dose for the second scenario (slow continuous release).

$$d_2(t) = \int_0^t c_2(\tilde{t}) * \dot{V}_{breathed} d\tilde{t} + \text{const}$$

$$d_2(t=0) \stackrel{!}{=} 0 \Rightarrow \text{const} = c(t_0) * \dot{V}_{breathed} * \left(\frac{1}{a} - \frac{1}{a+b} \right)$$

$$\Leftrightarrow d_2(t) = c(t_0) * \dot{V}_{breathed} * \left(-\frac{1}{a} * e^{-a*t} + \frac{1}{a+b} * e^{-(a+b)*t} + \left(\frac{1}{a} - \frac{1}{a+b} \right) \right)$$

By applying above functions, it is now possible to calculate the theoretical inhaled dose of chemotherapeutics assuming a continuous presence of a crew member over the whole application time (30 minutes).

Chemotherapeutics	Inhaled dose over a period of 30 minutes	
	Immediate release	Slow continuous release
Cisplatin (15 mg)	1,49*10 ⁻³ mg	1,36*10 ⁻⁴ mg
Doxorubicin (3mg)	2,99 *10 ⁻⁴ mg	2,72*10 ⁻⁵ mg

The chemotherapeutic dose applied during PIPAC is dependant of the body surface of the patient so that the results obtained can be directly compared to systemic chemotherapy doses.

Chemotherapeutics	Dose delivered*	
	Typical systemic dose	Inhaled dose
Cisplatin	150 mg	1,49*10 ⁻³ to 1,36*10 ⁻⁴ mg
Doxorubicin	30 mg	2,99 *10 ⁻⁴ to 2,72*10 ⁻⁵ mg

*assuming 2 square meter body surface.

Thus, the maximal inhaled dose in the worst case scenario after PIPAC application is expected to lie in the order of magnitude between 1:100'000 and 1:1'000'000 of a usual systemic dose. Any leakage scenario is expected to lie between these extreme boundaries.

The maximal potential exposition of the crew in the case of release of the toxic aerosol is minimal under the conditions described above. It has to be noted that the numbers given above are conservative since:

- the crew leaves the operating room during the application

- simulations with smoke showed that the laminar airflow directs smokes to the floor of the operating room so that a standing human person standing within the “clean area” will be prevented to inhale any toxic substance
- the immediate release scenario (worst case) is not realistic since the aerosol cannot be released all-at-once, the flow resulting from a leakage and not from an explosion.

Taking together, mathematical simulation of any possible leakage situations during PIPAC is showing that significant inhalative exposure of the operating crew to chemotherapeutic agents is extremely unlikely to occur and can be in practice excluded, even if the complete toxic aerosol is released from the abdominal cavity into the operating environment.

CRITICAL INCIDENT REPORTING SYSTEM (CIRS)

Between Nov, 2011 and Jan, 2015, our surgical and gynaecological teams at the Ruhr-University Bochum have performed over 650 PIPAC procedures. All scrub nurses have accepted to participate to the PIPAC procedures and the initial resistance of some employees has vanished. A two-person, specific safety checklist has been implemented which is systematically used before chemotherapy application, according to the 4-eyes principle. This checklist includes each important step of the procedure, in particular checking the tightness of the abdomen, the functionality of the laminar air-flow and proper connection of the CAWS. The checklist has largely contributed to the safety and to the acceptance of the procedure.

Two intraoperative incidents were reported and analyzed, within the framework of our CIRS (Critical Incident Reporting System). Both incidents were classified as minor because they did not cause any exposure of the personnel, and were caused by an accidental disconnection of the high-pressure line between the injector and the micropump.

Following measures were implemented:

- a protection sheet (analogous to a sterile sheet protecting the camera during laparoscopy) has been added to the safety system.
- the manufacturer of the equipment was required to provide the micropump sealed together with a high-pressure tubing, in order to exclude such disconnection in the future.

No severe incident, in particular no significant leakage of the chemotherapy aerosol has been registered, and no harm was caused to any participant. No patient injury caused by material and/or pressure was reported.

DISCUSSION

Chemotherapy is an essential component of modern, multimodal cancer therapy. However, many drugs used to treat cancer are known to be mutagenic, teratogenic and carcinogenic. Great caution has to be taken in the manipulation of these substances in order to

prevent any contamination of the environment and in particular of the team involved. In particular, special attention is traditionally given to the prevention of any chemotherapeutic aerosol. Therefore, it is all but a surprise that development of PIPAC has first raised concerns about the risk of occupational inhalation linked to the generation of toxic aerosols. To assess this problem, it was not possible to rely on existing safety standards, since PIPAC had not been performed before. However, we could compare – to some extent – intraperitoneal aerosol chemotherapy to aerosolized chemotherapy in lung cancer. In this latter setting, aerosolized chemotherapy had been delivered in a well-ventilated room with an air filtering system [19]. Alternatively, a mobile filter air cleaning system combined with a collecting tent has also been also effective in preventing propagation of aerosol during inhalation of nebulized liposomal cisplatin [16]. Chemotherapy concentration in the air remained below workplace exposure limits.

In fact, the problem of potential inhalative exposition of the operation room personnel is not specific to PIPAC at all. The operating room team is regularly exposed to toxic aerosols, in particular to toxic vapors generated by electrosurgery (reviewed in 25). The chemicals present in the greatest quantity in electrocautery smoke are hydrocarbons, nitriles, fatty acids and phenols [26]. Of these chemicals, carbon monoxide (CO) might be the most concerning: high levels of CO are produced during laparoscopic cholecystectomy [27]. CO production is of particular concern in laparoscopic procedures where smoke is trapped and concentrated in the peritoneal cavity. Electrocautery during laparoscopic procedures has been shown to increase intra-abdominal CO to ‘hazardous’ levels, leading to small yet significant elevations of carboxyhaemoglobin (COHb) [28]. Levels of CO in the intra-abdominal cavity at the end of a laparoscopic cholecystectomy have been found to be 100–1,900 parts per million (ppm) above the 35 ppm for a one-hour exposure set by the US Environmental Protection Agency (EPA) [29]. In addition, CO is readily absorbed from the peritoneum into the bloodstream, creating a route for systemic intoxication [30].

Other chemicals present in smaller quantities, but which are still of significant concern, include acrylonitrile, hydrogen cyanide, formaldehyde and benzene. Acrylonitrile is a colourless, volatile liquid that is absorbed easily through the skin and lungs and exerts its toxicity by liberating cyanide [31]. The Occupational Safety and Health Administration (OSHA) has set the upper limit of ambient exposure to this substance at 2ppm. Exposure levels of OR personnel have been shown to be 1–1.6ppm, just under the established limit [28]. Hydrogen cyanide is a toxic, colourless gas that is absorbed easily by the lungs, gastrointestinal tract and skin. It combines with ferric iron in cytochrome oxidase, thereby inhibiting cellular oxygen utilisation. In addition, it can act synergistically with CO in impairing tissue oxygenation. The US Department of Health and Human Services has set the short-term exposure limit at 10ppm. Levels in the ambient environment of the OR in one particular experiment were found to reach a mean of 5.7ppm and up to 10ppm, just at the allowed exposure limit [28]. Benzene has been proposed to be significantly responsible for the mutagenicity of electrocautery smoke.

The US NIOSH acknowledges the dangers of surgical smoke and recommends that smoke evacuation systems should be used where high concentrations of smoke and aerosols are generated. NIOSH has performed own investigations and bases recommendations on the finding of the mutagenicity of the airborne compounds collected during its evaluation and the acute health effects reported by OR personnel [32].

During PIPAC, a chemotherapy aerosol representing about 10% of a usual systemic dose is installed within the closed abdomen and removed through a closed suction system into the external environment. Our studies show that the risk of inhalative exposition of operating room personnel during PIPAC is reasonably low, since no traces of platin have been detected in repeated environmental analysis. Even in the worst case scenario, namely the complete release of the toxic aerosol into the environment, mathematical simulation shows a maximal inhaled dose of 1:100'000 to 1.1'000'000 over a period of time of 30 minutes. It has to be noted, however, that the effective inhaled dose in the worst case scenario lies in reality much lower than these numbers since:

- The repartition of the toxic aerosol is not homogeneous within the operating room, due to the direction of the laminar air flow down to the flow, so that a person standing next to the leakage point would be exposed only to a minimal fraction of the dose, if any
- Nobody is remaining within the operating room during the application period, since the procedure is remote-controlled.

In summary, this report shows that the risk of occupational exposure to chemotherapy during PIPAC has been reduced to a minimum so that the procedure is complying with German occupational safety regulations. In comparison with other surgical procedures – both open and laparoscopic surgery – where specific exposition of operating room personnel to toxic aerosols has been documented – PIPAC appears to be particularly safe. Thus, PIPAC can be applied on a regularly, daily basis in the clinical setting without exposing the personnel to cumulative doses reaching the long-term exposure limits. The safety conditions are given for performing Phase 2 and Phase 3 clinical trials in order to define the possibilities and limits of PIPAC in therapy of peritoneal carcinomatosis. However, following the implementation of all equipment, organizational aspects and procedures as described above, any other team starting with PIPAC should perform a toxicological work-place analysis. Environmental analysis should be scheduled at the very beginning of the routine application of PIPAC, and repeated in regular time intervals, in combination with biological monitoring.

Even though the data presented above are documenting a high level of safety during PIPAC, the potential risk of exposition of the personnel performing such procedures remains and would become real if the measures defined above are not implemented. As in other medical settings such as radioprotection, hygiene, etc., strict application of the standard operating procedures, repeated measurement of exposure levels and continuous education of physicians and nurses is necessary with the increasing use of this innovative and fascinating therapeutic strategy, in order to avoid any harm to the personnel.

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