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ORIGINAL ARTICLE

Occupational safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in an operating room without laminar airflow☆

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HIGHLIGHTS

- Random sampling in the air and from environmental items in operating rooms without laminar airflow were performed during our first PIPAC procedures.
- Only one sample out of 31 was moderately contaminated with cisplatin.
- PIPAC performed in operating rooms without laminar airflow might seem harmless for surgeons and their co-workers.

KEYWORDS
PIPAC;
Occupational safety;
Samplings;
Laminar airflow

Summary
Aim of the study: The safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) is often questioned when newly implemented in an operating room (OR); as it may increase the risk of exposure to cytotoxics for healthcare workers. There are no data on the risk of healthcare exposure in OR without laminar airflow. We aimed to ensure the safety of PIPAC for surgeons and their co-workers for newly implemented procedures in an OR without laminar airflow.
Patients and methods: Twenty-six samples with cellulosic wipes from surgeons and co-workers' environmental items and 5 specific polytetrafluoroethylene air-filtered collections were randomly performed for the first 2 cisplatin/doxorubicin-based PIPAC procedures in Strasbourg University Hospital. PIPAC was performed according to previously described safety protocol but without a laminar airflow and with an additional plastic cover and smoke evacuation device. Sampling and analyzes were performed by 2 accredited independent certified organizations.

☆ This study had been presented as a poster presentation at the PSOGI 2018 congress, Paris, September 9-11, 2018. The abstract is published in Pleura and Peritoneum 2018;1, Special Suppl, September 2018.

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Results: All air measurements were negative for cisplatin and doxorubicin. Only one wipe sample out of 26 was positive for cisplatin (4%) on the outer surgeon's pair of gloves but dosages on the surgeon's inner pair and hands were negative.
Conclusion: When performed in approved security conditions, even without laminar airflow, PIPAC might seem harmless for surgeons and their co-workers with very limited risk of exposure to cytotoxics.

Introduction

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) procedure is exponentially developing worldwide in the treatment of selected patients suffering from non-resectable peritoneal maligancies. Through a laparoscopic approach, this novel intraabdominal drug delivery modality allows a better drugs' distribution and tissue penetration compared to systemic chemotherapy. Most centers use Reymond et al. protocols [1—3] since its first description in 2011. The safety of PIPAC procedures is often questioned by the surgeon's co-workers when newly implemented in an operating room (OR), as it may increase the risk of exposure to cytotoxic. Exposure to cytostatics during PIPAC can be in the form of inhalation, direct or indirect skin or eye contact. Wearing gloves, protective clothing and glasses may prevent from cutaneous or ocular exposure. To prevent inhalation exposure, standardized occupational safety measures; with 3 levels of containment [1,4,5] are now well established. Level 1 implies an air-tight pneumoperitoneum, using balloon trocars and repetitive checking of the insufflator for any leaks. Level 2 is represented by the volume of the OR with air exchange through a laminar airflow ventilation. The third level consists in the remote application of the aersolized cytostatics from outside the OR, when the team leaves the room during the nebulization [5].

Several published studies already confirmed the absence of detection of cytotoxics in the air around the surgeon and the anesthesiologist, and little risk to exposure to platinum compounds in an OR with laminar airflow [6—9]. Yet, others showed that some contamination may be observed [9].

However, surgical teams that want to implement a PIPAC program in their department are not necessarily equipped with laminar airflow ORs, and one third of surgical teams already perform PIPAC in ORs without laminar airflow [2]. Nevertheless, in these conditions, no data exist on cytotoxic samplings from the environmental items of the OR. The harmlessness of the procedure in those conditions still needs to be proven. The objective of this study was to ensure the safety of PIPAC procedures on healthcare workers for newly implemented procedures in an OR without laminar airflow.

Patients and methods

Twenty-six samples with cellulosic wipes from surgeons' and their co-workers' environmental items and 5 filtered air collections were randomly performed during the first 2 cisplatin/doxorubicin-based PIPAC procedures (PIPAC 1 and PIPAC 2) in Strasbourg University Hospital, Strasbourg, France. Sampling and analyzes were performed by 2 accredited independent certified organizations (APAVE Alsacienne SAS, Mundoslheim, France and Toxilabo, Nantes, France). Air collections were performed in different locations on specific polytetrafluoroethylene (PTFE) filter and cytotoxics were quantified with a high-pressure liquid chromatography tandem mass spectrometry assay. Areal collections were performed with cellulosic wipes on 0.1 m^2 surfaces. Wipes were prepared by mineralization and cisplatin was quantified with an inductively coupled plasma-mass spectrometry. The laboratories limit values of detection were 0.00002 mg/m^3 for air samplings and 2.5 ng for wipe samplings.

PIPAC were performed in an OR without laminar airflow. PIPAC procedures were performed according to previously described techniques [1,10,11]. Briefly, under general anesthesia and in a supine position, two 12 mm balloon trocars (Kii© balloon, Applied Medical, Paris, France) were placed with an open laparoscopic approach. In order to limit handlings after the nebulization, and to ensure an air-tight pneumoperitoneum, resorbable aponevrotic sutures were placed for both trocars before the nebulization process. The pneumoperitoneum insufflation was 12 mmHg at room temperature and the absence of leak was repeatedly checked. An explorative laparoscopy was performed, the peritoneal carcinomatosis index and the volume of ascites were determined. Parietal nodules were biopsied, ascites was aspired and sent for cytology. A specific nebulizer (Capnopen©, Reger Medizintechnik, GmbH, Villingendorf, Germany) was introduced into the abdomen through a trocar under laparoscopic control and connected to a high-pressure injector (Accutron HP-D©, Medtron, Saarbrücken, Germany). As an additional precaution, since our OR was not equipped with laminar airflow; a transparent plastic cover protection connected to a smoke filtration device (PlumeSafe© Turbo, Buffalo Filter©, New York, USA) was used as an alternative to laminar airflow to aspirate potentially contaminated fumes with cytotoxics in case of a leakage. Cisplatin (7.5 mg/m^2) in combination with Doxorubicin (1.5 mg/m^2) were delivered to the OR as liquid solutions in closed plastic covers, prepared by the department of Pharmacy-Sterilization. The safety checklist protocols as described previously were double-checked before PIPAC administration [1,5,6]. We ensured that all equipment for abdominal closure was ready before leaving the OR. The drugs were loaded in the injector with their connections secured by a transparent cover sheet. Drugs were remotely aerosolized through the nebulizer for 5 minutes, and the system was kept 30 minutes at room temperature under an air-tight laparoscopic pneuperitoneum of 12 mmHg, with a permanent visual control of the nebulization and patients' vital signs (Fig. 1). Nobody entered the room during the administration time. All team members were wearing protective glasses (Safeview© eyewear

Figure 1. Final installation before PIPAC nebulization.

assembled glasses, Halyard©, USA), 2 pairs of gloves (Gammex® Latex powder free gloves, Ansell, Belgium), overshoes and high filtration FFP3 masks (3M™ Aura™ 1883+, 3 M France, Cergy-Pontoise, France). At the end of the procedure, the gas from the abdomen was removed through the closed surgical smoke evacuation system, by the surgeon who was the only person who entered the OR. After the exsufflation, trocars were removed and closure of the abdomen was performed. Only strictly necessary team members entered the room after skin closure.

Results

Air measurements were performed during PIPAC administration with a median length of 160 minutes [154—330] around the surgeon ($n = 1$), the OR nurse ($n = 1$), the anesthesiologists' induction room where the injector's remote control was placed ($n = 1$), the OR where the PIPAC was performed (with a distance of 1.5 meters from the patient $n = 1$), and a distant control OR without PIPAC ($n = 1$), as shown in Fig. 2. The median air volume collection was 321 L [320—665]. All concentrations of cisplatin and doxorubicin in the air were < 0.00002 mg/m^3, which corresponded to < 1% of the limit value of professional exposition.

Wipe sample spots are shown in the Fig. 2. Cellulosic wipe samples were performed on the OR floor under the operation table (before and after PIPAC 1 and 2, $n = 5$), on the PIPAC injector (before and after PIPAC 1 and 2, $n = 4$), on the cytotoxic protective cover (before PIPAC 2, $n = 2$), on the vacuum of the smoke filtration device (after PIPAC 1 and 2, $n = 2$), inside the plastic protective cover (after PIPAC 1 and 2, $n = 2$), on the surgeon's and OR nurse's shoes and overshoes (after PIPAC 2, $n = 4$), on the surgeons' and OR nurse's inside hands (after PIPAC 2, $n = 3$), and on the surgeons' and OR nurse's inside inner and outer pairs of gloves (after PIPAC 2, $n = 4$).

Twenty-five samples (96%) were < 2.5 ng/wipe for cisplatin. Only one sample (4%) on the outer surgeon's first pair of gloves after PIPAC 2 was positive for cisplatin (189 ng/wipe). However, cisplatin detection on the surgeon's second pair of gloves and hands wipes samples was negative.

Discussion

When implementing the first PIPAC procedure in our department, many members of the OR team were concerned by the safety of the procedure. For which, we were asked to demonstrate the safety of this procedure. Even with the pioneer team lead professor MA Reymond having published clear recommendations and safety protocols governing the PIPAC procedures, the available equipment for teams wanting to implement PIPAC in their institutes differs [1,5]. This is the case in our department, where we are not equipped with laminar airflow in our ORs. With the growing interest for this novel approach, and its expected benefits, the initial safety protocol will most likely be modified as we learn more and expand our knowledge about this new therapy technique.

We report here for the first time, cytotoxics samplings in the environmental items in ORs without laminar airflow during PIPAC procedures. These results may help other surgical teams to implement PIPAC in their own institutes. Cisplatin and doxorubicin were undetectable in the air during PIPAC.

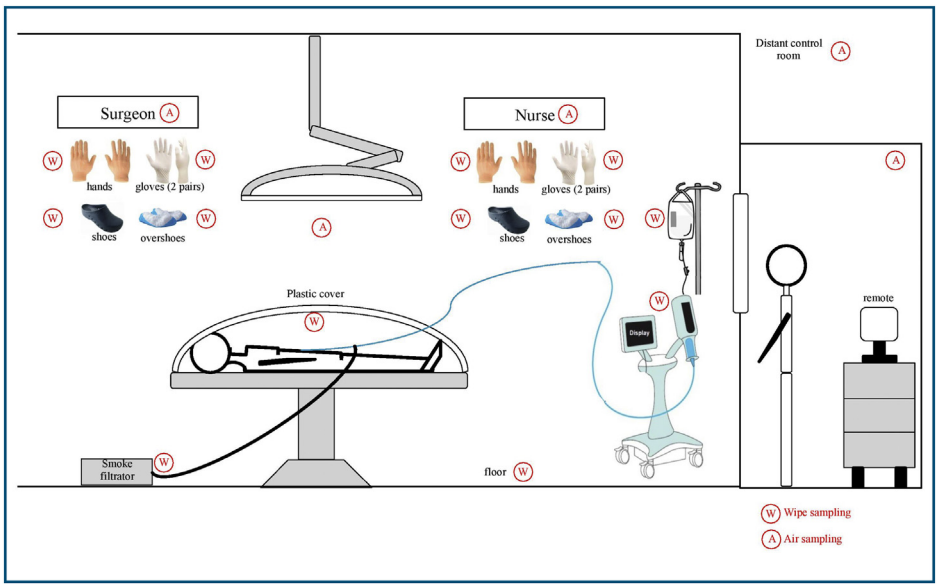

Figure 2. Illustration of the sampling spots.

Only one out of 26 wipe samples on the surgeon's first pair of gloves was positive for Cisplatin with moderate contamination. This contamination probably occurred during the trocar removal at the end of the procedure, as previously postulated by Ndaw et al. [9]. Closing the abdominal planes may thus represent the highest risk of exposure. However, the second pair of gloves and surgeon's hands were not contaminated. We showed here the safety of the procedure, even without laminar airflow. Healthcare workers exposure to cytostatics during PIPAC may result from inhalation, direct or indirect skin or eye contact. The 3 levels of containment (described earlier) may prevent from cytotoxic leakage and thus exposure during the PIPAC [5].

The use of the transparent cover protection is not a part of the original safety protocol that has been independently validated [1,5,6]. As a replacement of laminar airflow in level 2 containment, this transparent plastic cover may limit the risk of inhalation exposure in case of a leak. However, no cytotoxic trace was found on the plastic cover.

Furthermore, to insure no chemical air leaks to adjacent ORs occur; a neutral or negative pressure system must be installed in the OR [12]. This configuration requires an OR door airlock when entering to ensure the safety of the adjacent rooms [12].

Professor MA Reymond's team performed mathematical simulation to determine the degree of exposition to the team in case of a leak. Two scenarios were simulated: first scenario with an immediate and complete leak at the beginning of the PIPAC procedure, second scenario with a slow continuous release of the whole aerosol over time. In both scenarios, the concentration of the toxic substance in the air could be considered insignificant after 12 to 15 minutes from the start of the PIPAC procedure [13].

Furthermore, in the worst-case scenario, namely the immediate and complete release of the toxic aerosol into the environment, mathematical simulation showed a maximal inhaled dose of 1:100,000 to 1:1,000,000 of an usual systemic dose over a period of 30 minutes [13].

Thus, in case of a leak, a 30 minute pause should be respected before entering the OR.

Except for teams performing hyperthermic intraperitoneal chemotherapy, healthcare workers in an OR have generally no experience in cytotoxics' handling. However, by its simplicity, effectiveness and the low morbidity of the procedure, there is no doubt that PIPAC will be implemented in structures not necessarily specialized in peritoneal surface malignancies. Standardized protocols will facilitate the implementation of PIPAC programs, and certifying healthcare workers' to these types of surgeries will guaranty the safety of the procedure.

In conclusion, implementing a new PIPAC program questions the safety for surgeon's healthcare co-workers. When performed in approved security conditions, even without laminar airflow, PIPAC may seem harmless for the surgeons and their co-workers with very limited risk of exposure to cytotoxics. Further sampling studies may confirm these results.

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Disclosure of interest

The authors declare that they have no competing interest.

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