Intrathoracic aerosol chemotherapy via spray-catheter

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Abstract. Pressurized intrathoracic aerosol chemotherapy (PITAC) has been introduced to the clinical setting as a novel treatment option for pleural metastasis (PM). For decades the therapeutic application of aerosols was limited to intrabronchial delivery. However, present studies suggest performing PITAC on patients with PM and malignant pleural effusion. Using an established *ex vivo* swine model, the present study aimed to introduce a facilitated intrathoracic chemoaerosol application via spray-catheter. Using an ex-vivo model of 3 postmortem swine, the feasibility of intrathoracic aerosol chemotherapy (ITC) with doxorubicin using a spray-catheter was evaluated in a normal pressure environment. Following thoracotomy, the spray-catheter was inserted via trocar. Tissue samples were retrieved and further analyzed by fluorescence microscopy to detect doxorubicin contact. Our data demonstrated that the application of ITC was technically feasible and did not exhibit any significant obstacles. By making a minimally invasive thoracotomy incision it was possible to create an adequate pneumothorax without the need of a double-lumen tube or intubation. ITC did not require the creation of a pressurized environment. Tissue samples revealed doxorubicin contact within the pleura. In conclusion, ITC is a fast and feasible procedure that could possibly be administered via bedside application, therefore eliminating the need of an operating room and surgical staff. However, further studies are required to evaluate the safety of patients and physicians regarding this novel applicational modality. Nevertheless, the present study demonstrated that ITC may potentially be applied at bedside, an option that is particularly important for patients who do not qualify for PITAC procedures.

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Abbreviations: ITC, intrathoracic aerosol chemotherapy; MIP, micropump; MPE, malignant pleural effusion; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PITAC, pressurized intrathoracic aerosol chemotherapy; PM, pleural metastasis; PC, peritoneal carcinomatosis

Key words: pleural metastasis, malignant pleural effusion, chemo installation, peritoneal carcinomatosis, pressurized intrathoracic aerosol

Introduction

Both management and treatment options for pleural metastasis (PM) and malignant pleural effusion (MPE) are continuously evolving, as seen by the introduction of tunneled pleural catheters, chemical pleurodesis and combined procedures (1-3). PM is a common manifestation of several tumor entities exhibiting a poor prognosis (4-6). The treatment of PM is often interdisciplinary and includes oncologist, pulmonologists, surgeons, anesthesiologists and other specialists. Recently, pressurized intrathoracic aerosol chemotherapy (PITAC) has been introduced to the clinical setting as a modified version of the micropump© (MIP™; Reger Medizintechnik)-based pressurized intraperitoneal aerosol chemotherapy (PIPAC) (7). PITAC is currently used in PM patients who especially suffer from recurrent pleural effusions.

Two of the investigators of the present study have worked as physicians at the Department of General Surgery, Marien Hospital Herne (Herne, Germany), where PIPAC was introduced and where numerous patients have received PITAC treatment. Following PITAC treatment, patients exhibited good results with a significant decrease or even remission of MPE production in the pleural cavity. Currently, only limited clinical data is available on the efficacy of intrathoracic aerosol chemotherapy by means of PITAC (7). In its present form, PITAC is defined as a surgical procedure requiring an operation room, a defined amount of surgical personnel, such as a general or thoracic surgeon and surgical assistants, and

materials as well as the MIP™, a single-use, high-pressure injector pump.

However, these preconditions in conducting PITAC may limit the opportunity to extend its application on a larger scale in non-surgical disciplines. Therefore, it is important to investigate whether, from a technical point of view, it is possible to facilitate PITAC procedures and make them available for bedside applications. Technical studies on PIPAC procedures have already suggested that alternatives to the currently used MIP™ are possible (8,9) and its mode of operation could be improved (10,11).

In addition, studies have investigated the use of different substances (12) and new drugs (13) for PIPAC applications. However, since intraperitoneal aerosol chemotherapy is predominantly used by surgeons and gynecologists in cases of peritoneal metastasis, its potential for the treatment of PM and MPE has been of less research interest. Despite limited data on the incidences of PM and peritoneal metastasis, the occurrence of MPE's is assumed to be more widespread than PM, thus emphasizing the relevance of aerosol chemotherapy in patients with MPE. The present study aimed to demonstrate an easily applicable intrathoracic aerosol chemotherapy bedside approach for potential clinical use. The present reported version of intrathoracic aerosol chemotherapy has the potential to expand to disciplines other than thoracic surgery.

Materials and methods

Experimental set-up. Intrathoracic chemotherapy (ITC) was performed on three swine at 10 min post-mortem. All experiments were performed at the veterinary animal laboratories of Wroclaw University (Wroclaw, Poland). Swine were premedicated with an intramuscular injection of midazolam (0.1 mg/kg, Midanium 5 mg/ml; WZF Polfa S.A.), medetomidine (0.02 mg/kg, Cepetor 1 mg/ml; Cp - Pharma Handelsgesellschaft Mbh) and ketamine (8 mg/kg, Ketamina 100 mg/ml; Biowet Puławy Sp. z o.o.) mixture. Euthanization was performed via intravenous injection using sodium pentobarbital with pentobarbital (50 mg/kg with 12 mg/kg, morbital 133.3 mg/ml + 26,7 mg/ml; Biowet Puławy Sp. z o.o.) according to recommended protocols of the Handbook of Veterinary Anesthesia (14,15).

Experiments were conducted after a previous cardiovascular study on the swine. Fresh post-mortem swine cadavers were placed in a supine position and fixed at all four extremities. Using a scalpel, a small thoracic incision was made at the middle mediothoracic line. The parietal pleura was manually perforated, and a pneumothorax was established by placing a 5 mm trocar (Kii®Balloon Blunt Tip system; Applied Medical). Additionally, a 3 mm plastic tube was inserted through the trocar to maintain the pneumothorax and a normal pressure environment inside the chest and the surrounding environments. The surgical thoracotomy entrance site was sutured to prevent air leakage parallel to the placed trocar. To ensure that no leakage occurred during the experiment, a total of 200-300 ml air was pumped into the thorax at a pressure of 12 mmHg, resulting in a stable insufflation of the wall for a few min. Subsequently, a 3 mm plastic tube was inserted through the trocar to release any remaining pressure in the thorax. After this, the tube was removed, and the spray-catheter was placed into the trocar.

A doxorubicin solution (3 mg/50 ml NaCl 0.9%) was aerosolized and delivered into the thorax with a 10 ml syringe and a constant flow at 23˚C (Fig. 1).Five min after injecting the total doxorubicin solution, a chest tube was inserted through the trocar. The trocar was then removed from the chest and the chest tube was connected to a suction system with an intersecting drain bottle. Subsequently, 30 min after the described procedure, the thorax tube was removed, and the thoracic entrance site was completely sutured. The thorax was surgically opened via thoracotomy and a total of eight tissue samples were retrieved from each swine, including four tissue samples from the visceral pleura and four tissue samples from the parietal pleura.

Approval for the study was provided by The Ethical and Veterinarian boards at Wroclaw University of Life and Environmental Sciences (Wroclaw, Poland; approval no. 11/2018/P1).

Spray-catheter. The spray-catheter (PW-6C-1; Olympus Surgical Technologies Europe) consists of a connecting device and a high-pressure line connecting the shaft to the nozzle. The nozzle head has a small central opening and the spray-catheter generates a polydisperse aerosol. The spray-effect is achieved by manual pressure on the connecting syringe.

Microscopic analysis. Following treatments, tissue samples were rinsed with sterile 0.9% NaCl solution to eliminate superficial cytostatics and then immediately frozen in liquid nitrogen. Cryosections were prepared from the visceral and parietal pleura. Sections were mounted with VectaShield containing 1.5 μg/ml 4',6-diamidino-2-phenylindole (Thermo Fisher Scientific, Inc.) to stain nuclei. The penetration depth of doxorubicin was determined using a Nikon Eclipse 80i fluorescence microscope (magnification, x10; Nikon Instruments Europe BV). The distance between the luminal surface and the inner most positive staining for doxorubicin accumulation was measured and reported in μm (Figs. 2 and 3).

Statistical analysis. Experiments were independently performed three times and four tissue samples were retrieved from both the visceral and the parietal pleura, respectively. In total, three cryosections per tissue sample were subject to doxorubicin penetration measurements. Data is presented as the mean ± SD. Statistical analyses were performed using Sigma Plot (version 12; Systat Software, Inc.). Student's t-test by ranks was used to analyze groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Technical feasibility. No complications were observed during the procedures. ITC was applied in all three swine using a normal pressure environment. Each swine procedure was performed by one physician and one assistant in <1 h. The creation of an adequate pneumothorax via small thoracotomy was possible and conducted without using a double-lumen tube or intubation. The creation of a pressurized cavity was not required to establish an adequate working space for chemotherapeutic aerosol generation.

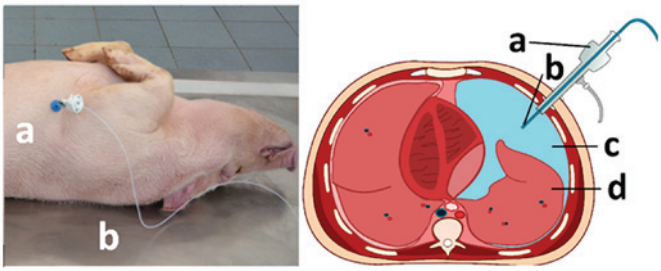

Figure 1. Application of intrathoracic aerosol chemotherapy. The left panel shows intrathoracic aerosol chemotherapy via (a) trocar on a swine. Following lung collapse, a highly concentrated chemosolution was injected into the thoracic cavity via (b) spray-catheter on the side of application. The spray-catheter (a) is introduced via a 5 mm trocar on the side. The right panel presents a transversal thoracic image of ITC with (c) pneumothorax and (d) a collapsed lung. (a) The trocar ensures mechanical stability of (b) the flexible spray-catheter during the process of insertion and application.

Intrathoracic chemotherapy. After placement of the chest tube and application of negative pressure, part of the applied chemotherapeutic solution was removed by the drainage system. Further thoracotomy revealed detection of some residual chemotherapeutic solution in the thoracic cavity. Therefore, removal of chemotherapeutic solution was incomplete. Tissue samples were retrieved from different sites of the pleural and visceral peritoneum. Following fluorescent microscopy, tissue probes revealed doxorubicin contact within all measured pleural locations. The mean tissue penetration rate was 540±186 μm for the visceral peritoneum and 224±97 μm for the pleural peritoneum.

Discussion

Currently, research on pressurized aerosol chemotherapy is of particular interest. Beside studies on technical features (16,17), biological efficacy (18) and clinical relevance (19), the search for other applicational modalities has received particular attention (20-23). PITAC is an example of an applicational modality that stretches beyond the current PIPAC. From the clinical experience of certain investigators, multiple patients receiving PITAC have demonstrated benefits from this therapy, which emphasizes its clinical efficacy, particularly in the treatment of MPE. However, the main clinical interest has been on PIPAC. This is rather attributable to factors surrounding PITAC than to its outcome or efficacy. In peritoneal metastasis, as opposed to PM, only few treatment options are available in palliative cases.

In both PM and MPE treatment, a variety of different catheters are used depending on the procedure performed, for example, liquid chemotherapy installations or surgical procedures, such as pleurectomy and talc poudrage (4). PITAC is currently performed in the operating room and requires the use of a MIP™, a high-pressure injector and specifically trained surgical personnel. However, many patients with PM or MPE may not have access to a surgical department or surgical time may not be allotted toward PITAC procedures. Smaller and less complicated PIPAC approaches have already been demonstrated (8). The question remains as to whether it is technically feasible to reduce the components of the MIP™ and the high-pressure injection device, as well as change the pressurized environment for the intrathoracic procedure.

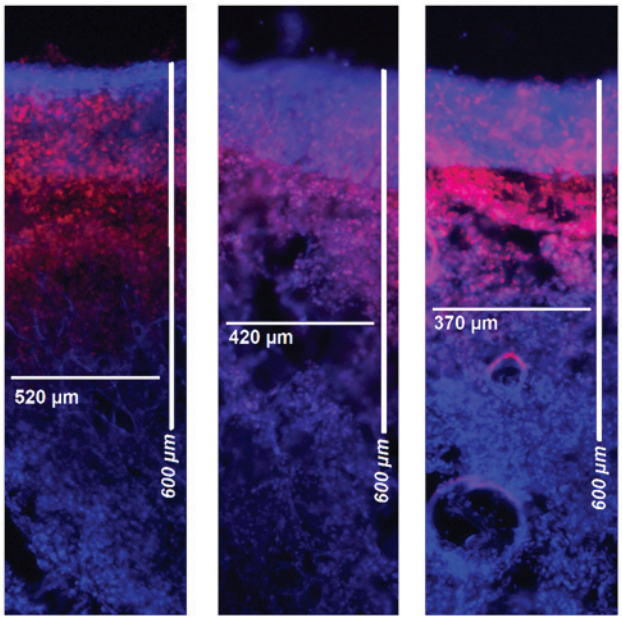

Figure 2. Representative visceral pleura samples from the lung. Doxorubicin penetrating from the visceral pleura at the top into the deeper lung tissue in the samples. Intranuclear doxorubicin is marked in red. Blue areas are background color from contrasting DAPI.

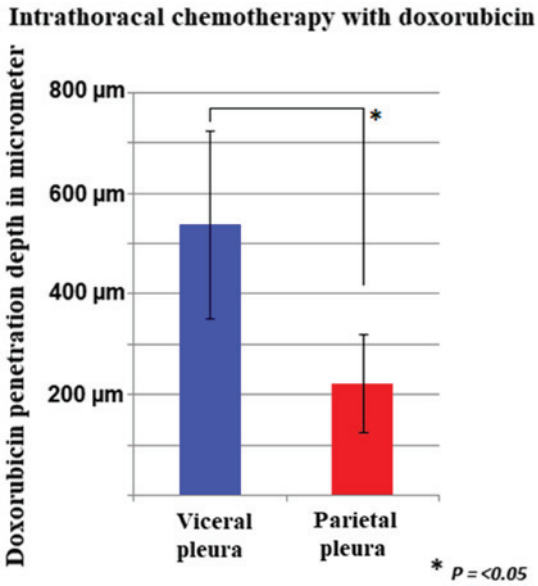

Figure 3. Mean doxorubicin depth in parietal and visceral pleura following intrathoracic aerosol chemotherapy in a postmortem swine model. *P<0.05..

From a technical point of view, a bedside approach is feasible without needing the MIP (19). Rather, the currently less expensive spray-catheter may be used instead. If these procedures are proven safe from an occupational perspective, this finding may alleviate the need for an operation room. The application of such procedures may be open to other non-surgical doctors as they could use ITC for the treatment of PM and MPE. Aerosol chemotherapy could be administered bedside by any doctor who could be assisted by

a nurse, nurse assistant or medical student. While PIPAC technologies require a pressurized abdominal cavity, there is no such prerequisite for intrathoracic applications. Current data on the effect of pressure on chemoaerosol penetration rates is conflicting. While some studies report increased cytotoxicity with increased pressure applied (24), other studies do not demonstrate any such effect on drug penetration rates (25).

However, these effects must be studied in a clinical setting. The application of ITC via spray-catheter could be a novel and technically feasible option for the treatment of PM and MPE. More studies must be performed to thoroughly study both patient and personnel safety in possible bedside applications. However, one must be aware that bedside or outpatient conditions are different from experimental conditions. Thus, the mere technical feasibility of an approach may not equate to its applicability in the clinical setting. Possible complications of mini-thoracotomies, such as pneumothorax through lung-fistula as well as local and pleural infections, must also be considered with this approach. Additionally, the need for sufficient analgesia must be considered for bedside applications. If studies on safety aspects indeed indicate that bedside applications of this technique are safe, this could help to extend this procedure to other non-surgical disciplines. Extending this technique to other fields could assist with the collection of important clinical data to investigate its efficacy. Since current clinical data on PIPAC present promising results, similar results are expected for ITC treatment in patients with PM with or without MPE. However, further studies are required, and the ITC approach requires further evaluation to be used in PM and MPE treatment.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

VK, MP, KN and JK performed the statistical analysis, acquired the data and drafted the manuscript. AM designed the study, acquired the data and drafted the manuscript. RP designed and supervised the study, interpreted the data and critically revised the manuscript for important intellectual content. MA and TK substantially contributed to the conception of the study design, supervised the study, and drafted and critically revised the manuscript for important intellectual content. TK moreover performed data interpretation and gave final approval for publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approval for the study was provided by the Ethical and Veterinarian boards at Wroclaw University of Life and Environmental Sciences (Wroclaw, Poland; approval no. 11/2018/P1).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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