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Pressurized Intra-peritoneal Aerosol Chemotherapy (PIPAC) *via* Endoscopical Microcatheter System

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Abstract. *Background/Aim: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) is becoming an increasingly widespread approach for delivering intra-peritoneal chemotherapy (IPC) by means of a chemoaerosol. Currently, the aerosol dispersion is achieved by using a special micropump (MIP®). However, the delivery of a chemoaerosol into the abdominal cavity is not limited to the MIP®. This study aimed to investigate the feasibility, drug penetration and distribution of PIPAC via an established endoscopical microcatheter (MC). Materials and Methods: An established ex vivo PIPAC model containing native fresh tissue samples of swine peritoneum was used to aerosolize doxorubicin at a pressure of 12 mm Hg CO_2 at 27° degrees Celsius. On the top cover of the PIPAC chamber a MC device was installed via trocar. Tissue specimens were placed as follows: at the bottom of the plastic box (A), at the side wall (B), at the top (C) and the covered bottom (D) of the box. In-tissue doxorubicin penetration was measured using fluorescence microscopy on frozen thin sections. Results: The mean depth of doxorubicin penetration was found to be significantly higher in tissue directly exposed to the aerosol jet. All samples had contact with doxorubicin. Penetration rates were: A: 348 (+/– 47 μm), B: 174 (+/– 64 μm), C: 92 (+/– 27 μm) and D: 84 (+/– 45) μm. Conclusion: Our ex vivo data suggest that PIPAC can be delivered via MC device. While local drug penetration is practically congruent to known PIPAC performance with MIP®, the MC offers a feasible, flexible, easy to handle and economic improvement compared to conventional PIPAC.*

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Peritoneal metastasis (PM) is a manifestation of advanced digestive-tract and gynecological cancers. Patients with PM of non-gynecological malignancies have a poor prognosis with median survival rates ranging from 4 to 10 months (1). However, a combination of cytoreductive surgery (CRS) and heated intra-peritoneal chemotherapy (HIPEC) offers a curative approach to PC in a highly selective group of patients with isolated peritoneal cancer (2-5). However, intra-peritoneal chemotherapy (IPC), CRS and HIPEC have major technical and prognostic limitations. Beside high local complication rates regarding application devices for IPC, only a limited number of patients with PM qualify for a surgical approach with CRS and HIPEC. Patients with diffuse and irresectable PM and high Peritoneal carcinoma index score (PCI) do not show improved prognosis after HIPEC and other IPC procedures if complete resection has not been achieved (6).

Pressurized intra-peritoneal aerosol chemotherapy (PIPAC) has been introduced as a new approach that overcomes limitations of IPC with liquid solutions (7) and improves performance in patients with diffuse PM (8, 9). Anti-tumoral effect of IPC is strongly limited by poor penetration (<1 mm) of anticancer drugs into peritoneal nodules (10, 11). The limited diffusion of IPC is attributed to the peritoneum - a high interstitial tumor pressure (12), tumor barrier (13), and the capillary system, that supports the availability of drugs within the tumor tissue. Improved penetration and distribution qualities are achieved by using an aerosol-creating device which produces highly concentrated drug particles in form of a "therapeutic chemo-aerosol" within the capnoperitoneum. Currently, this aerosol-creating device is the micropump (MIP®, Reger Medizintechnik, Rottweil, Germany). The performance of the PIPAC with MIP® has been intensively

studied in multiple *ex vivo* (14, 15) and animal models (16). Penetration (14), distribution (17) as well as biological and technical features have been examined (18, 19). Even the technical construction as well as the granulometric outburst have been characterized and studied in full length. Main fluid volume in MIP® is directly deposited by gravitational sedimentation and therefore these particles impact at the opposite side of the spray jet (20). Technical principles and factors influencing particle size, distribution and penetration characteristic have been discussed and analyzed in multiple *ex vivo* and animal experiments (21, 22). Currently, the main challenge is to improve the PIPAC procedure by using a new aerosol-creating device. The need for a new aerosol-creating device is pressing. The MIP creates an inhomogeneous drug distribution which has been extensively investigated by means of tissue penetration measurement of doxorubicin and peritoneal scintigraphy (23, 24). The single nozzle of the MIP in the original technology of PIPAC is stiff and thus restricted in movement, marking a major limitation. Material and purchasing cost of PIPAC can be quite high. Furthermore, concerns of having no hands-on and clinical experience in handling the technology and potential difficulties might intimidate surgeons from applying PIPAC. Therefore, alternative aerosol-generating devices are developed and examined to meet these concerns (18, 25, 26). Current difficulties with these new and recently published prototype devices include that these are even less investigated than the original (MIP®). Yet, the common goal of these devices is to especially overcome the distribution inhomogeneity in PIPAC that has become apparent in previous studies. Such an alternative device for PIPAC may already be in practice at every national and international hospital and medical center. Aerosol generators and microparticle-creating pumps are already widely used in daily practice. However, these applications were not initially made for PIPAC. While some of these devices are far older than the MIP®, they may have the potential to overcome its limitations. A flexible endoscope with a build-in microcatheter (MC) that is currently used by general surgeons, gastroenterologists and pulmonologist could be an easily-applicable, cost-effective alternative to the MIP® while it may also overcome the current limitations of the MIP®. To evaluate whether it is feasible to perform PIPAC using an endoscopical MC, the previously described, well known *ex vivo* box model. By doing so, we were able to evaluate the performance of the MC regarding maximum tissue penetration and distribution of aerosolized doxorubicin.

Materials and Methods

Ex vivo PIPAC model. The experiments were performed in a standard *ex vivo* model on commercially available tissue samples, therefore no approval of the Institutional Review Board and no consent of the Local Board on Animal Care were necessary. The *ex vivo* PIPAC model has been well established and previously described in many studies (17, 20). A commercially available hermetic plastic box with a total volume of 3.5 liter, mimicking the abdominal cavity, was used. In the center of the top cover of the plastic box, a 5 mm trocar (Kii®Balloon Blunt Tip System, Applied Medical, Rancho Santa Margarita, CA, USA) was placed. Using one trocar, the nozzle of the MC was introduced. Four fresh tissue specimens of peritoneum (German land race pigs), each measuring 3.0×3.0×0.5 cm, were placed as follows: (A) bottom of the plastic box, (B) side wall and (C) top cover, and (D) margin of the aerosol jet covered with a bilaterally open tunnel (Figure 1). The plastic box was then tightly sealed and a constant CO_2 capnoperitoneum of 12 mmHg (Olympus UHI-3, Olympus medical life science and industrial divisions, Olympus Australia, Notting Hill, Australia) was established and maintained throughout each single procedure. A total of 3 mg of Doxorubicin (Doxorubicin hydrochlorid was purchased from PFS®, 2 mg/ml, Pfizer, Sandwich, United Kingdom) was dissolved in 50 ml NaCl 0.9% and aerosolized at room temperature (27˚C). Then the tissue specimens were exposed to the doxorubicin aerosol for 30 min (exposure phase).

Microcatheter (MC, PW-205V Olympus Surgical Technologies Europe, Hamburg, Germany). The MC consists of a connecting device, a pressure line connecting the shaft to the nozzle. The nozzle head has a small central opening. A total of 50 ml Doxorubicin solution (3 mg/50 ml) is manually delivered with a 10 ml syringe at a constant flow (1 ml per second). A refill syringe is connected to the side of the injecting syringe so the entire dose can be given without the need to readapt to a new syringe. The MC generates a polydisperse aerosol. Following the application, samples are left in the *ex vivo* box for 30 min. At the end of the PIPAC procedure, the MC and the tissue specimens were retrieved from the plastic box.

Microscopic analysis. After treatments, all tissue samples were rinsed with sterile NaCl 0.9% solution in order to eliminate superficial cytostatics and immediately frozen in liquid nitrogen. Cryo sections (7 μm) were prepared from 10 different areas of each specimen. Sections were mounted with VectaShield containing 1.5 μg/ml 4',6-diamidino-2-phenylindole (DAPI) to stain nuclei. Penetration depth of doxorubicin was monitored using a Nikon Eclipse 80i fluorescence microscope (Nikon Instruments Europe B.V. Amsterdam, Netherlands). The distance between the luminal surface and the innermost positive staining for doxorubicin accumulation was measured and reported in micrometers.

Statistical analyses. Experiments were independently performed three times. A representative amount of tissue sections for each sample were subjected to doxorubicin penetration measurement. The statistical analyses were performed with Sigma Plot 12 (Systat Software Inc., California, USA). The Kruskal-Wallis One Way Analysis of Variance on Ranks was used to compare independent groups. Descriptive statistics include mean, median and percentiles.

Results

Immediately after the start of the aerosol phase, the humidity reached 100% and remained constant during the entire procedure. Fluorescence microscopic analysis of the different tissue specimens revealed a significant difference regarding the penetration depth of doxorubicin (Figure 2). A maximum

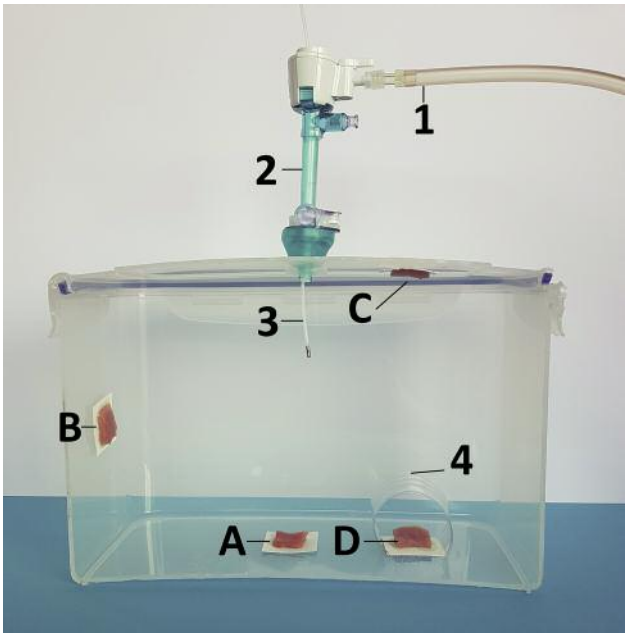

Figure 1. *Laparoscopy-assisted ex vivo experiment on fresh swine peritoneum for investigation of spatial distribution pattern of aerosolized doxorubicin during PIPAC therapy. For better demonstration, the front wall of the plastic box (ex vivo PIPAC model) has been removed. MC is placed in the center of the top in a 5 mm trocar. 1) insufflation tube, 2) trocar 3) MC 4) bilateral open tunnel. Tissue samples A, B, C and D at different locations of the box.*

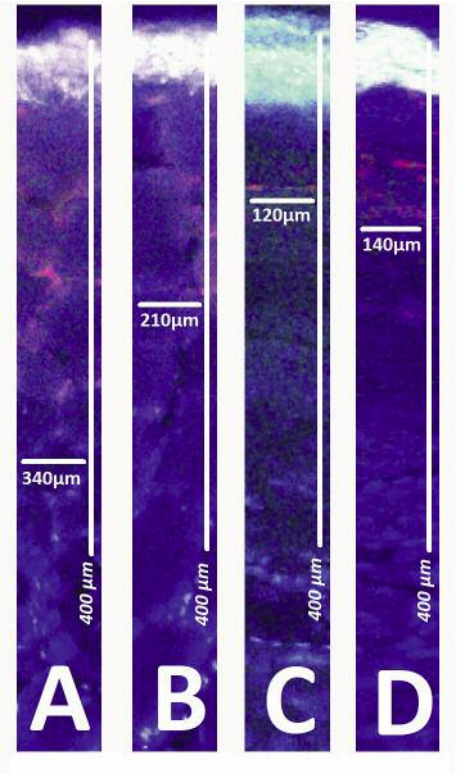

Figure 2. *Microscopic analysis of penetration depth of doxorubicin (red) into fresh peritoneal tissue samples of German land race pigs. Nuclei (blue) were stained with 4',6-diamidino-2-phenylindole (DAPI). Left to right: Bottom (A), wall (B), top of the box (C) and bottom covered (D).*

of drug penetration was observed in peritoneum directly exposed to the aerosol jet. Penetration rates were: (A) 348 (+/– 47 µm) (B) 174 (+/– 64 µm), (C) 92 (+/– 27 µm) and (D) 84 (+/– 45) µm (Figure 3). The highest measured single tissue penetration was 480 µm in one tissue sample. The lowest measured single penetration was 0 µm. The highest mean penetration depth was observed in the non-covered tissue samples at the bottom of the plastic box. Although this performance of MC shows a macroscopically visible difference in the distribution pattern, all areas were in contact with doxorubicin. The difference between the penetration at sample A and the samples B, C, D in the periphery was significant with $p<0.05$ (A *versus* B) and even more so with $p<0.01$ in (A *versus* C) and (A *versus* D).

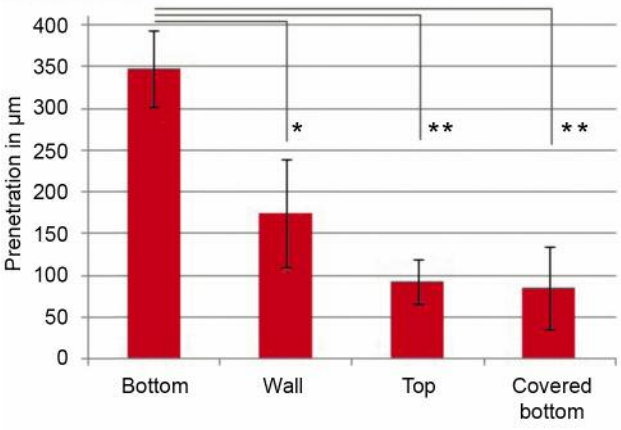

Figure 3. *Doxorubicin penetration and distribution within the box. *p<0.05, **p<0.01.*

Discussion

IPC delivered as a pressurized aerosol has been introduced as a new and innovative approach to improve the treatment of advanced, multi-resistant PM. The concept of PIPAC has shown to overcome some limitations observed by conventional intraperitoneal chemotherapy with liquid solution. PIPAC was found to have good clinical outcomes in patients with PM (8, 9). With regard to the latest published studies, it is known today that aerosol-creation and application into the peritoneal cavity is neither biologically nor technically

restricted to the MIP® (18, 22, 25). The creation of new aerosol-producing devices is becoming increasingly popular in contemporary research (18, 26). With regards to untrained personnel, high costs and uncertainty in the handling of PIPAC with MIP®, this study aimed to investigate a new option to apply PIPAC using of a well-known FDA-approved MC which has been utilized in gastroenterology and pulmonary medicine for years. One of the great benefits of the MC is its already wide usage in endoscopy. The safety aspects of intraperitoneal aerosol technology by means of a microinjection element have been previously studied (27) for the mono component nozzle pump like the MIP®.

The distribution results in our standard *ex vivo* model are very close to prior well studied PIPAC models with MIP® (17). Medium tissue penetration levels of 215 μm ±79 μm were detected in the tissue sample at the bottom and 34 μm ±19 μm were detected in the tissue sample in the bilaterally open plastic tunnel. As chemotherapy is directly injected at the target site, the large droplet sizes as well as the low air flow in the capnoperitoneum during aerosol phase lead to direct impaction of the peritoneum due to gravitation. The smaller particles which are not instantly subject to gravitational force move to more peripheral target sites and collide with the local peritoneum there. It is noteworthy that the MC has the additional advantage of moving the head of the nozzle in every desired direction to ensure more equal drug distribution, an important aspect which is not feasible with the stiff MIP®. This additional freedom of movement may significantly improve performance and possibly solve the problem of inhomogeneity if the nozzle positions are changed during the injection. This finding confirms expectations and limitations of the current one nozzle technology in PIPAC as previously reported (21, 22). Still our findings have significant implications with respect to the daily practice of PIPAC therapy. It has been suggested that in clinical practice, PIPAC is restricted to the application of MIP® which bears known disadvantages such as limited PIPAC treatment centers that offer MIP®-Technology, affordability due to single-use application of the MIP®, experience with the MIP® as well as other limitations regarding drug distribution pattern and in-tissue penetration. This study offers a possible alternative medical device that has been used for decades in daily practice, making it easily-acceptable, cost-friendly and easy to use. Based on our findings and prior experiments (18, 22, 25), it becomes evident that the PIPAC application is not limited to the MIP®. In daily practice, alternative pump and application systems may also be used with the ultimate goal of achieving higher local penetration and drug concentrations. The concept of single injection pump with a mono component nozzle technology for PIPAC has been extensively studied and discussed. Turbulent airstream, convection as well as gravitation are driving the distribution of the aerosol particles (22). The limitation of the single-nozzle technology could be overcome by the rotating head in the endoscopical approach, an aspect which requires further in-detail investigation. Although good results have been documented for MIP® regarding safety (27), these would need to be investigated for PIPAC with the MC as well since identical results cannot be automatically assumed. These previous findings indicate that the application of a chemoaerosol by a microinjection element is safe. The MC is practically universally available at any hospital and its usage is well-known with long-term clinical experience. Exchanging the MIP with an MC seems to be a possible and feasible alternative that requires further investigation. The MC can change the position of the nozzle and therefore redirect the main particle stream into different directions to improve distribution. Moreover, in MC assisted PIPAC, a single trocar entrance can be used for both the MC and the camera as opposed to the two trocar entrances currently used in PIPAC with MIP®. Currently, the cost of the MC device is significantly lower than that of the MIP® device. Overall, the MC needs to be studied more intensively with regard to its possible use in aerosol chemotherapy. The application of the MC in PIPAC also needs further research with regards to establishing a standard protocol in daily practice.

Conclusion

Our data indicate that PIPAC *via* endoscopic catheter is possible and offers many advantages over conventional PIPAC. PIPAC with MC should be considered for clinical application and thus must be more thoroughly studied in the future. Until today, extensive clinical experience has been gathered in the daily clinical work with endoscopical MC devices. While the results of our study are promising, a possible routine application of MC in PIPAC requires a more thorough investigation.

Conflicts of Interest

The Authors have no conflicts of interest or financial ties to disclose.

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