Surgical Endoscopy (2019) 33:3503–3510
https://doi.org/10.1007/s00464-019-07043-y

NEW TECHNOLOGY

Assessment of the aerosol distribution pattern of a single-port device for intraperitoneal administration of therapeutic substances

Rafael Seitenfus[1,6] · Antonio Nocchi Kalil[1] · Eduardo Dipp de Barros[1] · Claudio Galeano Zettler[2] · Gabriel Oliveira dos Santos[2] · Olivier Glehen[3] · Carlos Humberto Cereser Junior[1] · Paulo Roberto Walter Ferreira[4,5]

Received: 27 January 2019 / Accepted: 24 July 2019 / Published online: 1 August 2019

Abstract

Background In the last 20 years, intraperitoneal chemotherapy (IPC) has been explored as a modality for the management of peritoneal metastases of gynecologic, gastrointestinal, and primary peritoneal tumors. Direct delivery of chemotherapeutic agents to the peritoneal cavity space has proved superior to systemic chemotherapy when evaluating characteristics such as drug concentration reached in the peritoneal space, penetration into peritoneal metastases, and chemotherapy-related toxicity. Traditionally, IPC is delivered by peritoneal lavage with a liquid solution. This form of delivery has limitations, including inhomogeneous intraperitoneal distribution and limited ability to penetrate tissues and metastatic nodules. An alternative mode of delivery is so-called pressurized intraperitoneal aerosol chemotherapy (PIPAC). Within this context, the present study sought to identify the pattern of spatial distribution of therapeutic solutions aerosolized into the peritoneal space using a single-port PIPAC device and ascertain whether the aerosolized method is superior to the traditional (liquid) mode of IPC delivery.

Methods Analysis of the rate of intra-abdominal staining with aerosolized 2% silver nitrate in five porcine models.

Results Assessment of differences in stain impregnation between the upper, middle, and lower abdomen did not reveal significant differences ($p = 0.42$). The median sum scores were 1 for the upper abdomen and 3 for the middle and lower abdomen.

Conclusions Aerosolization does not reach all regions of the abdomen homogeneously. However, adequate exposure of the upper abdomen, mid-abdomen, and lower abdomen to chemotherapeutic agents can be achieved with PIPAC.

Keywords Peritoneal carcinomatosis · Aerosol · Medical device · Pressure · Pressurized intraperitoneal aerosol chemotherapy (PIPAC) · Innovation

In the last 20 years, the combination of intraperitoneal chemotherapy and cytoreductive surgery has become a consolidated approach to control peritoneal spread of cancer and treat peritoneal metastases in several malignancies. In this new management paradigm for carcinomatosis, intraperitoneal chemotherapy plays a particularly important role. Direct infusion of chemotherapeutic agents into the intraperitoneal space has proved superior to isolated systemic chemotherapy in the treatment of peritoneal disease [1]. The direct action of the drug on metastatic nodules in the peritoneal cavity carries several advantages when evaluating characteristics such as drug concentration reached in the peritoneal space, penetration into peritoneal metastases, and chemotherapy-related toxicity [1]. Traditionally, IPC is delivered by peritoneal lavage with a liquid solution carrying the chemotherapeutic agent. This form of delivery has limitations regarding tissue penetration capacity and intraperitoneal distribution [2]. A new mode of delivery has emerged as an alternative to traditional administration

✉ Rafael Seitenfus
rafasei@hotmail.com

1 Surgical Oncology Service, Hospital Santa Rita, Santa Casa de Misericórdia, Porto Alegre, RS, Brazil

2 Pathology and Cytology Service, Hospital Santa Rita, Santa Casa de Misericórdia, Porto Alegre, RS, Brazil

3 Department of Surgical Oncology, Centre Hospitalier Lyon-Sud, Hospices Civils De Lyon, Pierre-Benite, France

4 Graduate Program in Engineering, Innovation and Entrepreneurship, Faculdade de Desenvolvimento do Rio Grande do Sul (FADERGS), Porto Alegre, RS, Brazil

5 Bhio Supply, Esteio, RS, Brazil

6 Rua Dario Pederneiras, 354/204, Porto Alegre, RS 90630-090, Brazil

of liquid solutions into the peritoneal cavity: pressurized intraperitoneal aerosol chemotherapy (PIPAC) [3]. Early evidence suggests this method provides superior tissue penetration and a more homogeneous distribution within the peritoneal space. The possibility of multiple administrations and the lower morbidity of the procedure, which is performed laparoscopically, make PIPAC a promising approach for the treatment of peritoneal carcinomatosis. Encouraging initial results have been obtained in the treatment of peritoneal carcinomatosis secondary to gastric [4], colon [5], ovarian [6], and pancreatic cancer [7].

Within this context, the present experimental study was designed to describe and evaluate the spatial distribution of this new form of chemotherapy delivery in the peritoneal space, using a single-port paradigm to carry out all steps involved in the procedure.

Materials and methods

Ethical aspects

This study was approved by the local Research Ethics Committee (protocol no. 407). All procedures followed the ethical principles established by the Brazilian Society for Laboratory Animal Science (SBCAL/COBEA). In addition, this study followed the Canadian Council of Animal Care (CCAC) guidelines, the Brazilian Guidelines for the Care and Use of Animals for Scientific and Educational Purposes (CONCEA Resolution No. 25 of 29 September 2015), and the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.

Study design and statistical analysis

This cross-sectional, in vivo, experimental study was designed to evaluate the distribution of silver salts in the peritoneum of five pigs (*Sus scrofa domesticus*, Mammalia: Suidae). The data obtained were entered into an Excel spreadsheet and exported for statistical analysis in SPSS 20.0. Variables were described as medians and ranges (minimum–maximum), and the Friedman and Kruskal–Wallis tests were used for comparison. The significance level was set at 5%.

Experimental protocol and areas of analysis

The five animal models underwent intraperitoneal aerosolization of 2% silver nitrate stain, delivered by the unidirectional BhioQap device, version 3 (ANVISA registration no. 80381210067). All animal models underwent the same systematic operative procedure, which included application of therapeutic pneumoperitoneum to a pressure of 12 mmHg for 30 min. Throughout the surgical procedure, the animals were kept anesthetized by vivarium staff veterinarians. After the established period, all animals underwent laparotomy and biopsies obtained from three broadly defined regions of the abdomen: the upper abdomen, the middle abdomen, and the lower abdomen. Each of these regions was composed of sub-regions of interest previously defined by the researchers, on the basis of observations made during a previous experiment in March 2017 [8]. The upper abdomen was divided into five sub-regions: right dome of the diaphragm, left dome of the diaphragm, lesser omentum, anterior stomach, and posterior stomach. The middle abdomen was also divided into five sub-regions: right paracolic gutter, omentum, proximal jejunum, distal ileum, and left paracolic gutter. The third region (lower abdomen) was divided into four sub-regions: right iliac fossa, bladder wall, cul-de-sac, and left iliac fossa. Biopsies were obtained from each of these sub-regions; specimens were immediately fixed in formalin and sent for histopathological examination. The data obtained through histopathological evaluation were used to calculate a silver nitrate staining for each sub-region. The values obtained in each sub-region of the abdomen were then added to yield a general score of the three different regions (upper, middle, and lower abdomen).

Aerosolization and experimental substance

Aerosolization is the mechanical process of transforming a liquid into microdroplets, creating a mist of aerosolized fluid. For this study, the aerosolization process was performed using a BhioQap model 3 device (Bhiosupply), registered with the Brazilian National Health Surveillance agency (ANVISA no. 80381210067), connected to an ACIST Empower CTA injector system (Bracco).

Silver nitrate diluted in 200 mL distilled water to a concentration of 2% was the solution selected to evaluate the spatial distribution of the aerosol within the peritoneal cavity. The choice of silver nitrate is due to the fact that it fixes silver salts in any tissues with which it comes into contact. These salts are then readily detected by microscopy. This makes it possible to identify whether a given sample came into contact with the aerosolized substance.

Procedure

The five animals were anesthetized by staff veterinary anesthesiologists at the vivarium. All were then subjected to the same procedure, which was divided into four stages. The first step was to prepare the live swine model for diagnostic laparoscopy. Each anesthetized animals were placed in dorsal recumbency on an operating table, with the limbs and tail restrained. The second stage was begun with a supraumbilical incision (Hasson's technique) and placement of the

BhioQap trocar. Pneumoperitoneum was established with a laparoscopic insufflator (Stryker) until the intra-abdominal pressure reached 12 mmHg, as for routine conventional laparoscopy. At this stage, the double silicone ring seal was evaluated to ascertain whether the cavity was adequately sealed. The third step consisted of using the BhioQap unidirectional device for aerosolization of the intraperitoneal chemotherapy solution, with the aid of a mechanical arm to secure the 10-mm optic (Fig. 1).

All animals underwent 2% silver nitrate aerosolization through the BhioQap device, respecting a 30-min period of therapeutic pneumoperitoneum with a stable intra-abdominal pressure of 12 mmHg. The aerosolization process was carried out at a flow rate of 3 mL/s and a pressure of approximately 300 psi. The fourth stage consisted of peritoneal biopsies. Once aerosolization was complete, a conventional laparotomy was immediately performed in each animal to obtain biological specimens, which were fixed in formalin for later histopathological analysis.

Histological analysis

This stage was carried out by the Pathology team at Hospital Santa Rita, Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre. The samples were cut into cross sections 3–4 mm thick and stained with eosin to measure the degree of silver impregnation in the tissues of interest, taking the mesothelial surface as a reference. To better distinguish blackened color of silver salts against the tissue and to prevent false positives, hematoxylin was not used. The degree of silver impregnation was evaluated by simple (optical) microscopy and classified as follows: (0) Impregnation absent—No impregnation of silver salts in the mesothelial surface; (1) Weak impregnation—Limited impregnation of silver salts, corresponding to the a heterogeneous monolayer, visible on at least 10% of the mesothelial surface; (2) Moderate impregnation—Intermediate accumulation of silver salts, corresponding to a continuous (homogeneous) monolayer visible on up to 80% of the mesothelial surface, without overlapping silver residues (Fig. 2); and (3) Strong impregnation—Marked accumulation of silver salts, corresponding to a continuous (homogeneous) monolayer visible on more than 80% of the mesothelial surface, or by formation of silver salt aggregates on more than one layer of tissue (Fig. 3).

Results

All animals were alive at the end of the experiment. None showed any signs of hemodynamic instability throughout the procedure, especially during injection of the test substance. Aerosolization was considered adequate and the whole proposed process was completed in all five animals. A good abdominal seal was maintained throughout the procedure in all animals, with a stable pneumoperitoneum at 12 mmHg obtained for at least 5 min before PIPAC. This pressure remained stable throughout the 30-min therapeutic pneumoperitoneum period. In each animal, the intra-abdominal distribution pattern of the aerosol was divided into the three previously established major regions of the abdomen. Each region was assigned a score ranging from 0 to 3 according to the findings of histopathological examination (0, no staining; 1, slight staining; 2, moderate staining; 3, marked staining). Thus, the maximum possible score for each of the three regions was 15 for the upper abdomen, 15 for the middle

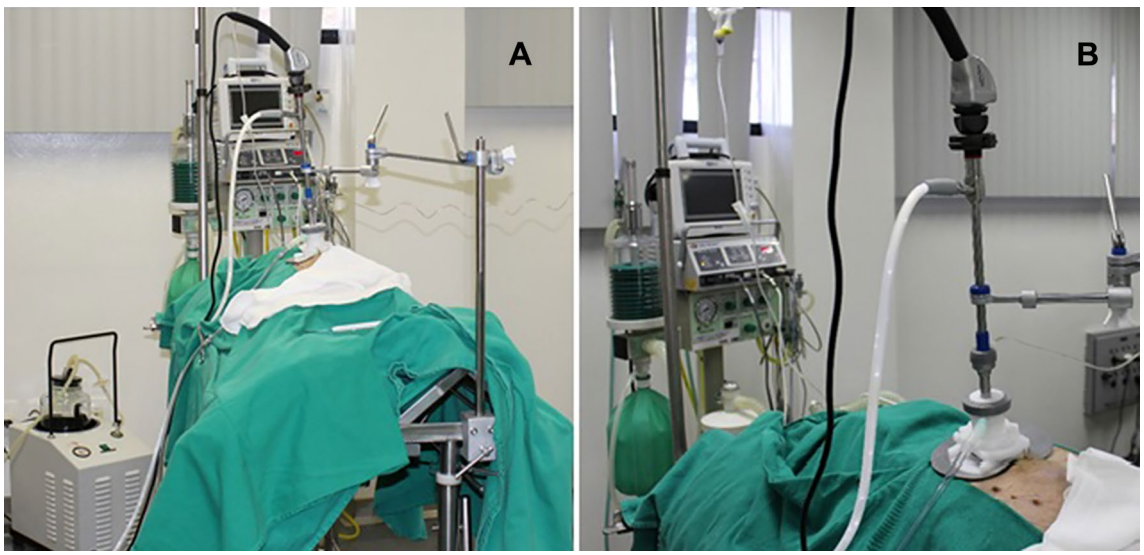

Fig. 1 BhioQap device. **A** Overview and **B** mechanical arm

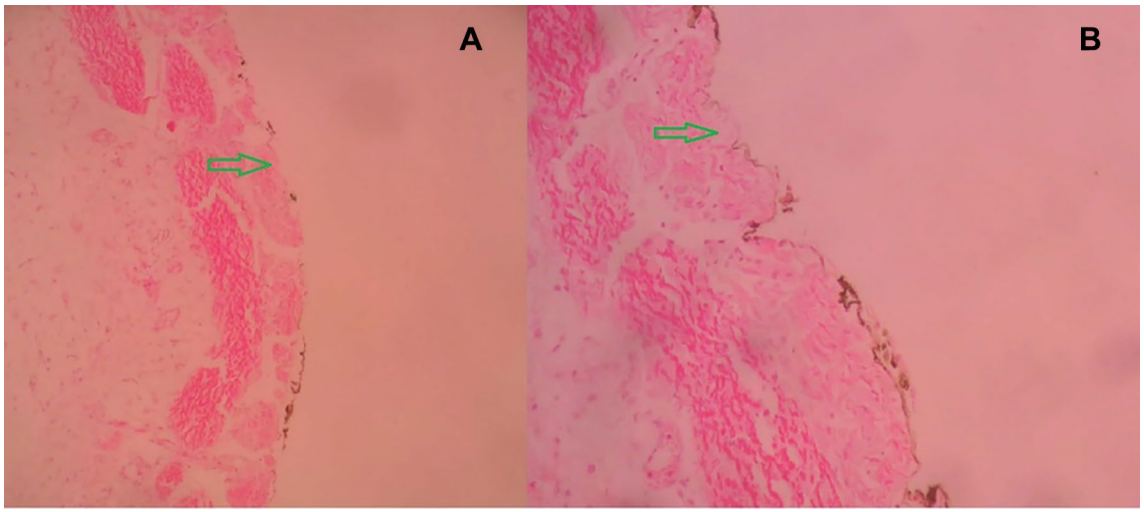

Fig. 2 Histological analysis of silver nitrate impregnation into the tissues of interest. **A** Weak impregnation. Arrow denotes a heterogeneous layer of staining in more than 10% of the tissue. **B** Moderate impregnation. Arrow denotes a homogeneous layer without overlapping silver residues

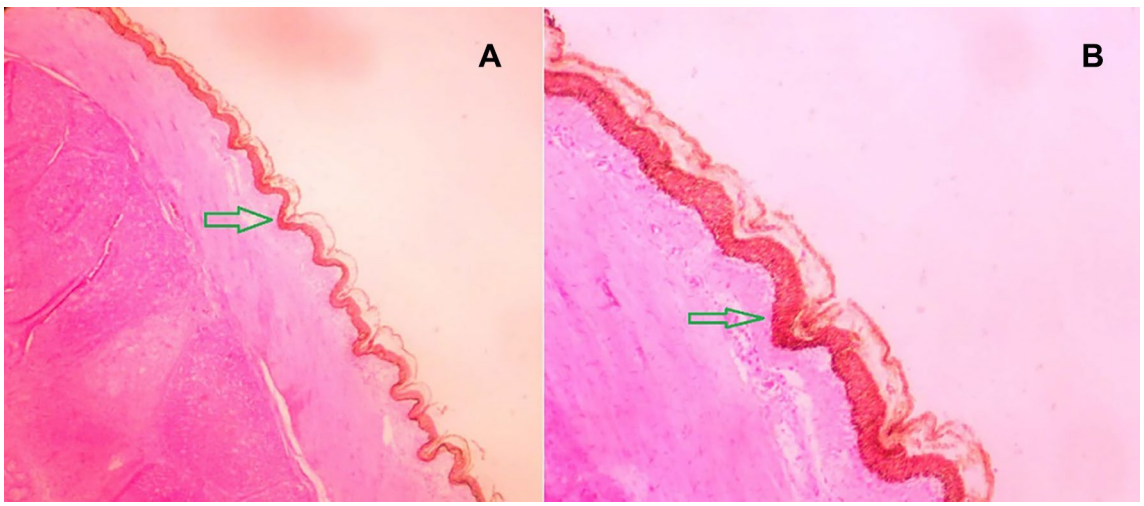

Fig. 3 Histological analysis of silver nitrate impregnation into the tissues of interest. **A** Strong impregnation (×40). Arrow shows overlapping layers as well as a homogeneous monolayer on the surface. **B** Larger magnification (×100)

abdomen, and 12 for the lower abdomen. Table 1 shows the distribution pattern found in each of the five animals.

The overall median staining score, considering all of the animals, was 1 for the upper abdomen, corresponding to slight staining (range 0–3). For the middle and lower abdomen, the median scores were 3, corresponding to strong staining (range 0–3 as well). The median scores found in each region of the abdomen (upper, middle, and lower) in each of the animals, and their respective ranges (minimum–maximum), are shown in Table 2.

The upper, middle, and lower regions of the abdomen in each animal were added to obtain an overall staining score for each region, as well as compared to each other in each animal. Animal 1 exhibited a significant difference ($p=0.03$) in staining, suggesting lower impregnation of the upper abdomen when compared to the middle and lower abdomen in the same animal. The remaining animals did not show any significant difference in silver impregnation scores when the three predefined regions were compared among one another (animal 2, $p=0.77$; animal 3, $p=0.47$; animal 4, $p=0.09$; animal 5, $p=0.08$). When testing for differences in impregnation among the five animals in each specific region (upper abdomen, middle abdomen, and lower abdomen), no statistically significant difference was observed (upper

Table 1 Staining score in the three major regions of the abdomen (upper, middle, and lower) and their respective sub-regions

	Upper abdomen	Right dome of diaphragm	Left dome of Diaphragm	Lesser omentum	Anterior stomach	Posterior stomach	Middle abdomen	Right gutter	Omentum	Jejunum	Ileum	Left gutter	Lower abdomen	Right iliac fossa	Bladder wall	Cul-de-sac	Left iliac fossa
Animal 1	5	0	2	0	0	3	10	0	3	3	3	1	12	3	3	3	3
Animal 2	4	0	0	0	1	3	8	0	3	3	0	2	6	3	0	3	0
Animal 3	4	1	3	0	0	0	12	3	0	3	3	3	6	3	0	3	0
Animal 4	8	3	3	0	2	0	7	0	2	0	2	3	9	3	3	0	3
Animal 5	13	1	3	3	3	3	12	3	2	3	3	1	3	0	0	0	3
Score	Regional staining	Microscopic staining score					Regional staining	Microscopic staining score					Regional staining 1	Microscopic staining score			

0: No staining. 1: Slight staining. 2: Moderate staining. 3: Marked staining

Table 2 Median (min–max) staining score for each region of the abdomen

Animal	Upper abdomen	Middle abdomen	Lower abdomen
Model 1	0 (0–3)	3 (0–3)	3 (0–3)
Model 2	0 (0–3)	2 (0–3)	1.5 (0–3)
Model 3	0 (0–3)	3 (0–3)	1.5 (0–3)
Model 4	2 (0–3)	2 (0–3)	3 (0–3)
Model 5	3 (1–3)	3 (1–3)	0 (0–3)

abdomen, $p = 0.17$; middle abdomen, $p = 0.52$; lower abdomen, $p = 0.27$). Therefore, we pooled all per-region staining scores of the five animals into a single sum score for each region to assess whether there was a significant difference in staining between the upper abdomen, middle abdomen, and lower abdomen. The result revealed no significant difference ($p = 0.42$). The median sum scores were 1 for the upper abdomen and 3 for the middle and lower abdomen.

Discussion

The primary goal of intraperitoneal chemotherapy is to increase exposure of peritoneal metastases to the chemotherapeutic agent, thus decreasing both systemic and intra-abdominal effects [9]. During this process, adequate delivery of intraperitoneal chemotherapy throughout the abdominal cavity is a key determinant in obtaining optimal results to control one of the possible routes for dissemination of digestive, gynecologic, or primary peritoneal tumors. The pathogenic process of carcinomatosis follows a cycle of interaction between neoplastic cells and peritoneal tissue, leading to the activation of inflammatory mechanisms and, eventually, generation of fibrosis and adhesions [3]. This means the carcinomatous peritoneal cavity poses a natural obstacle to the adequate distribution of chemotherapy to all possible spaces within the abdomen in which peritoneal metastases may be protected and perpetuated. Over the course of more than 40 years of progress in intraperitoneal chemotherapy, modalities that can potentiate both the effect and distribution of agents have been developed. In 2000, Reymond et al. conceptualized that liquid chemotherapy might be converted into a therapeutic mist that would enhance both tissue penetration and distribution of the solution in the peritoneal space [3]. When a liquid substance is aerosolized, it takes on the same general behavior and distribution properties of a gas [2]. A homogeneous, rapid distribution in the physical space in which the gas is contained improves the distribution of the therapeutic solution [2]. Methods previously used for the delivery of chemotherapy in the peritoneal space used liquid carriers. Experimental and mathematical models have shown limited exposure of the peritoneal surface when

using peritoneal dialysis solutions to expose the peritoneum to therapeutic substances. When peritoneal dialysis solution was infused into the rodent abdomen with methylene blue and bovine albumin, postmortem specimens indicated that large areas of visceral and parietal peritoneum had little or no evidence of exposure to the test solutions [10]. Several areas in particular are more susceptible to inadequate exposure, such as portions of the cecum, small intestine, colon, and diaphragm [2]. PIPAC appears to provide a more homogeneous and adequate alternative for delivery of chemotherapy to the peritoneal space [2]. Initial animal studies of the distribution of therapeutic mist in the abdominal cavity of porcine models demonstrated a distribution advantage for the PIPAC method when compared to use of liquid dialysis solutions as carriers [2]. Our sample shows the broad distribution behavior of the test solution when aerosolized into the pig peritoneal cavity. In all five animals in our sample, at least 25% of the area of interest (upper abdomen, middle abdomen, and lower abdomen) was impregnated with the 2% silver nitrate solution. Whether this rate of exposure enables appropriate treatment of different abdominal regions should be explored more intensively in future research.

Contradicting the initial evidence that PIPAC provided a homogeneous distribution, Khosrawipour et al. showed greater penetration and more homogeneous distribution of the drug within the area of direct spread of the PIPAC spray, and a shallower, more heterogeneous distribution in the area exposed to the therapeutic mist [11]. Another key determinant of the activity of aerosolized chemotherapy is the size of the aerosol droplet. The aerosolization spectrum will vary with the size of the droplets dispersed in the therapeutic mist. Aerosolization is already widely explored in medical practice as an alternative method for drug delivery in the respiratory tract. This experience can serve as a guide for delivery of chemotherapeutic agents with the PIPAC technique. It is known that droplets larger than 5 µm directly act on and settle in the upper airways. Droplets smaller than 2 µm are ideal for reaching more peripheral areas of the airways [12]. These characteristics may also be determinants of the effectiveness of PIPAC for treatment of peritoneal carcinomatosis. The portion of the therapeutic aerosol mist containing droplets larger than 10 µm is more likely to contact tissues directly. Thus, it delivers higher doses of chemotherapy to tissues directly exposed to the radius of action of the aerosol jet, but contributes little to a more homogeneous distribution of the agent in the peritoneal cavity. Conversely, the portion of the therapeutic mist consisting of droplets with a diameter < 1 µm behaves like a gas, providing a greater contribution to the distribution of the agent across the peritoneal cavity, but delivering a lower dose of chemotherapy [11]. Except for animal 1, none of the animals in our sample showed a significant difference in stain distribution across the three abdominal regions evaluated. However, when we assessed the difference in median score considering all regions of the abdomen in all five animals studied, we noticed a reduction in staining rate when comparing the upper abdomen (1, weak) to the middle abdomen (3, strong). This reinforces the hypothesis posited by Khosrawipour that regions directly exposed to the chemotherapy jet in the center of the abdomen are exposed to the therapeutic agent to a greater extent. The regions farthest from the center jet are more susceptible to the action of the smaller particles contained in the therapeutic mist [11]. In a previous study carried out for validation of the first version of the BhioQap aerosolization device, we explored a multidirectional delivery concept in an attempt to minimize the central jet effect described. We identified a broad pattern of intra-abdominal distribution, but without any homogeneity of impregnation of the test substance into the peritoneal surface. Dispersion of the test substance remained erratic, despite our attempt to circumvent the disadvantages of unidirectionality in the aerosolization pattern [8].

Analysis of the particle-size distribution of the therapeutic mist produced by the PIPAC device reinforced previous findings suggesting that droplet size plays an essential role in the dispersion capacity of the therapeutic mist within the peritoneal cavity. Larger droplets are highly susceptible to deposition, due to gravitational action and inertial impaction (> 5 µm), whereas droplets closer in size to the micron range (< 1 µm) play a more important role in diffusion of the aerosolized substance [13]. Direct granulometric analysis of the aerosolization pattern of the device evaluated by the German group led by Göhler et al. suggested that the dominant portion of the aerosol (97.5% of the therapeutic mist) was composed of medium-sized droplets (3 µm), thus directly related to gravitational deposition and inertial impaction [13]. This is a determinant of a more consistent treatment halo, spreading outward in a 15-cm diameter from the site of PIPAC application [13]. These findings raise the possibility that, even if PIPAC enhances intra-abdominal distribution of the therapeutic substance, there will still be areas relatively inaccessible to treatment, making distribution of the substances administered by this technique in the peritoneal cavity markedly heterogeneous. Our findings reinforce this notion of heterogeneous distribution, particularly in the upper abdomen. In addition to its distance from the radius of action of the aerosol produced by the PIPAC device, the upper abdomen presents anatomical features that make this space a challenge to aerosolization-based peritoneal treatment. The presence of the lesser sac and lesser omentum, protected by the lobes of the liver, pose a particular challenge to drug exposure in the upper abdomen. As shown in Fig. 4, even with marked impregnation of the anterior aspect of the liver, the lesser omentum remains “protected” from exposure to the therapeutic mist.

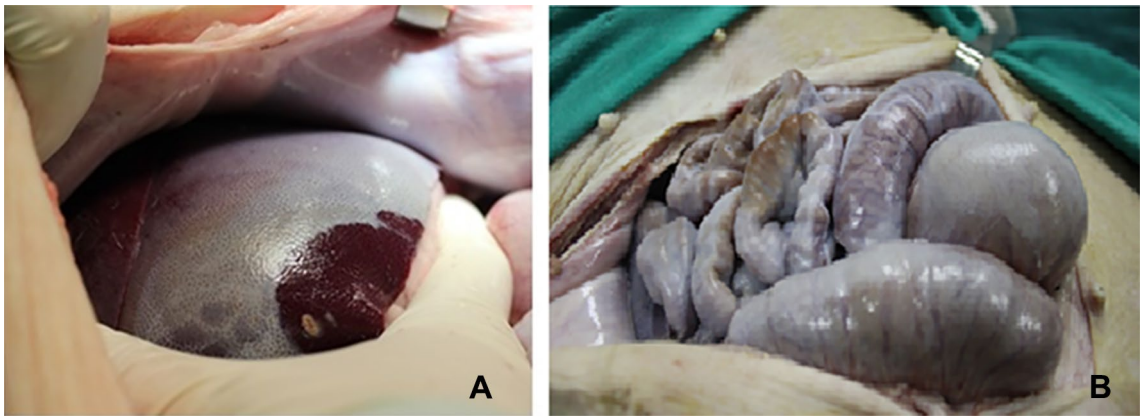

Fig. 4 Intraoperative view. Impregnation in the upper (**A**) and middle abdomen (**B**)

Surprisingly, the lower abdomen exhibited a median dye score of 3, suggesting marked impregnation in this region, even though it is distant from the central jet, as discussed above. Bellendorf et al. carried out a scintigraphic peritoneography analysis of the distribution of a tracer radionuclide in the swine abdomen and identified a trend toward concentration in the central part of the abdomen (small intestine and paracolic gutters) and cul-de-sac. Their distribution data closely resemble those obtained in our sample. However, the authors did not raise any hypothesis regarding the high concentrations observed in the cul-de-sac [14]. In our view, this is attributable to the natural pattern of deposition of liquid contents in the abdomen. A 30-min exposure of the peritoneal cavity to an aerosolized substance will lead to a natural formation of liquid contents, which will settle in the pelvis, increasing exposure of this region to the substance of interest.

Compliance with ethical standards

Disclosures Drs. Seitenfus, Kalil, Barros, Glehen, and Mr. Ferreira hold patents on the BhioQap device used in this study. Mr. Ferreira is employed by Bhiosupply, which manufactures and distributes the device. The other authors (Drs. Zettler, dos Santos and Cereser Junior) report no conflicts of interest.

References

1. Markman M (2003) Intraperitoneal antineoplastic drug delivery: rationale and results. Lancet Oncol 4(5):277–283
2. Solass W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA (2012) Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc 26(7):1849–1855. https://doi.org/10.1007/s00464-012-2148-0
3. Reymond MA, Hu B, Garcia A, Reck T, Kockerling F, Hess J, Morel P (2000) Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. Surg Endosc 14(1):51–55
4. Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D, Quenet F, Glehen O, Bakrin N, Passot G (2017) Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. Eur J Surg Oncol 43(11):2178–2183. https://doi.org/10.1016/j.ejso.2017.09.010
5. Demtroder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA (2016) Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis 18(4):364–371. https://doi.org/10.1111/codi.13130
6. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond MA (2015) Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: a cohort study. Anticancer Res 35(12):6723–6729
7. Khosrawipour T, Khosrawipour V, Giger-Pabst U (2017) Pressurized intra peritoneal aerosol chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLoS ONE 12(10):e0186709. https://doi.org/10.1371/journal.pone.0186709
8. Seitenfus R, Ferreira PRW, Santos GOD, Alves RJV, Kalil AN, Barros ED, Glehen O, Casagrande TAC, Bonin EA, Silva Junior EMD (2017) A prototype single-port device for pressurized intraperitoneal aerosol chemotherapy. Technical feasibility and local drug distribution. Acta Cir Bras 32(12):1056–1063. https://doi.org/10.1590/s0102-865020170120000007
9. Sampson JA (1931) Implantation peritoneal carcinomatosis of ovarian origin. Am J Pathol 7(5):423–444 **(439)**
10. Flessner MF (1996) Small-solute transport across specific peritoneal tissue surfaces in the rat. J Am Soc Nephrol 7(2):225–233
11. Khosrawipour V, Khosrawipour T, Diaz-Carballo D, Forster E, Zieren J, Giger-Pabst U (2016) Exploring the spatial drug distribution pattern of pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann Surg Oncol 23(4):1220–1224. https://doi.org/10.1245/s10434-015-4954-9
12. Rubin BK (2010) Air and soul: the science and application of aerosol therapy. Respir Care 55(7):911–921
13. Gohler D, Khosrawipour V, Khosrawipour T, Diaz-Carballo D, Falkenstein TA, Zieren J, Stintz M, Giger-Pabst U (2017) Technical description of the microinjection pump (MIP((R))) and granulometric characterization of the aerosol applied for pressurized intraperitoneal aerosol chemotherapy (PIPAC). Surg Endosc 31(4):1778–1784. https://doi.org/10.1007/s00464-016-5174-5
14. Bellendorf A, Khosrawipour V, Khosrawipour T, Siebigteroth S, Cohnen J, Diaz-Carballo D, Bockisch A, Zieren J, Giger-Pabst

U (2018) Scintigraphic peritoneography reveals a non-uniform (99 m)Tc-Pertechnetat aerosol distribution pattern for pressurized intra-peritoneal aerosol chemotherapy (PIPAC) in a swine model. Surg Endosc 32(1):166–174. https://doi.org/10.1007/s00464-017-5652-4