A prototype single-port device for pressurized intraperitoneal aerosol chemotherapy. Technical feasibility and local drug distribution[1]

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Abstract

Purpose: To evaluate the technical feasibility and homogeneity of drug distribution of pressurized intraperitoneal aerosol chemotherapy (PIPAC) based on a novel process of intraperitoneal drug application (multidirectional aerosolization).

Methods: This was an in vivo experimental study in pigs. A single-port device was manufactured at the smallest diameter possible for multidirectional aerosolization of the chemotherapeutic drug under positive intraperitoneal pressure. Four domestic pigs were used in the study, one control animal that received multidirectional microjets of 9 mL/sec for 30 min and three animals that received multidirectional aerosolization (pig 02: 9 mL/sec for 30 min; pigs 03 and 04: 3 mL/sec for 15 min). Aerosolized silver nitrate solution was applied for anatomopathological evaluation of intraperitoneal drug distribution.

Results: Injection time was able to maintain the pneumoperitoneum pressure below 20 mmHg. The rate of moderate silver nitrate staining was 45.4% for pig 01, 36.3% for pig 02, 36.3% for pig 03, and 72.7% for pig 04.

Conclusions: Intra-abdominal drug distribution had a broad pattern, especially in animals exposed to the drug for 30 min. Our sample of only four animals was not large enough to demonstrate an association between aerosolization and a higher silver nitrate concentration in the stained abdominal regions.

Key words: Injections, Intraperitoneal. Aerosols. Neoplasm Metastasis. Carcinoma. Swine.

■ Introduction

Peritoneal carcinomatosis is considered to be an advanced neoplastic disease for which the available treatments do not significantly alter the fatal outcome of the disease. In the past 20 years, however, the therapeutic approach to this condition has undergone significant changes. A better understanding of the condition as part of the process of cancer spread and as a disease limited to a single 'organ' – the peritoneum – has changed the forms of treatment of the disease[1]. This new concept, developed from the studies of Dr. Paul H. Sugarbaker, has led to different directions of approach for patients with peritoneal carcinomatosis in gastrointestinal tract, gynecological and primary peritoneal cancer. The combination of cytoreductive surgery and intraperitoneal chemotherapy (IPC) has been the key element in the attempt to control the disease. Administration of the chemotherapeutic agent directly into the intraperitoneal cavity has provided results superior to those of systemic chemotherapy when considering characteristics such as drug concentrations in the peritoneal cavity, penetration in peritoneal metastases, and toxicity of the chemotherapy[2]. Direct contact of the chemotherapeutic agent in the peritoneal cavity with the metastatic nodules has a higher bioactivity in the tumors than does systemic chemotherapy, demonstrating an advantage of intraperitoneal application for the treatment of carcinomatosis[3].

Traditionally, IPC consists of peritoneal lavage with a liquid solution carrying the chemotherapeutic agent. This form of application is limited by a non-homogeneous drug distribution in the abdominal cavity and poor tissue penetration[4]. A new application modality has emerged in recent years as an alternative to the conventional method of intra-abdominal application of chemotherapy, namely pressurized intraperitoneal aerosol chemotherapy (PIPAC)[5]. Aerosolization of the chemotherapeutic drug under positive intraperitoneal pressure has shown advantages over the use of liquid solutions for application of chemotherapy in the intraperitoneal cavity[6]. Due to the initial encouraging results with PIPAC in patients with peritoneal carcinomatosis in gastric cancer[7], colorectal cancer[8], and ovarian cancer[9], there has been a growing interest in the use of PIPAC as a possible treatment modality for this disease.

Within the context of the treatment of peritoneal diseases, we have developed a prototype drug delivery system, with features not yet explored in the process of application of PIPAC with the existing devices. The present preclinical study was therefore designed to describe the technique, feasibility and spatial (intraperitoneal) drug distribution of PIPAC based on a novel process of intraperitoneal application (multidirectional aerosolization) of therapeutic substances.

■ Methods

The study was approved by the local Research Ethics Committee (protocol nº 407). Animal handling and experimentation followed international standards and guidelines for the care and use of laboratory animals and the Brazilian ethical principles of animal experimentation. All efforts were made to minimize pain and discomfort, as well as to use only the minimum number of animals required to produce reliable scientific data. This study followed the recommendations of the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE Guidelines).

This was an *in vivo* experimental study in pigs. Four domestic pigs (*Sus scrofa domesticus*) were used in the study, one control animal that received multidirectional microjets and three animals that received multidirectional aerosolization. The pig was chosen as the experimental animal model for

this study because of the resemblance to human anatomy. The porcine model is also considered suitable for laparoscopic procedures.

Aerosolization and substance of interest

Our equipment uses a mechanical process associated with compressed air at constant flow that compresses the liquid under pressure through narrow holes for a short period of 15-20 seconds. This process leads to the formation of a therapeutic aerosol. The aerosolization process occurs by means of a mechanism developed in partnership with a Brazilian company (Bhio Supply, Esteio-RS, Brazil). It is based on the concept of aerosolization currently used in fuel injection nozzles and commercial aerosol products. A line attached to a pressurized injection system is used to push the therapeutic liquid into the equipment, named BhioQap. Aerosolization occurs by a mechanical process of passing the pressurized liquid through microtubules where the liquid comes into contact with an angled line with a constant CO_2 flow. This mechanism accelerates the particles and converts the liquid into aerosol.

Silver nitrate (4 g) diluted in 200 mL of distilled water (2% silver nitrate) was the solution of choice for assessing the spatial drug distribution of PIPAC. Silver nitrate, when in contact with tissues, leaves silver salts as a by-product in the sample, which are easily detectable by microscopy, thus allowing us to identify whether or not the sample was in contact with the substance.

Animal model

Four pigs (*Sus scrofa domesticus*) weighing 25 to 30 kg each were operated on under general anesthesia on March 30, 2017, at the laboratory animal facility of our institution. All animals were anesthetized by the same team of veterinary anesthesiologists and subjected to the same surgical procedure. The difference between animals lies in the method used for application of 2% silver nitrate and in the duration of exposure to the therapeutic solution.

Pig 01 (control) was exposed to microjets while pigs 02, 03, and 04 were exposed to aerosolization with compressed air. The injection time and velocity in the aerosolization process was evaluated at two different time intervals; the total duration of exposure, however, was set at 15 min and 30 min as initially proposed. In pig 02, the solution was aerosolized at an injection flow rate of 9 mL/sec and compressed air was injected at a constant flow for the same period. In pigs 03 and 04, the solution was aerosolized at an injection flow rate of 3 mL/sec and compressed air was injected at a constant flow for the same period. This difference was required to detect the most feasible method for *in vivo* models. The two injection parameters were obtained from previous *in vitro* experiments conducted at the Bhio Supply laboratories. Table 1 summarizes the parameters used for application of PIPAC in the four porcine models.

Table 1 - Parameters used for application of intraperitoneal chemotherapy.

Porcine model	Type of application	Pneumoperitoneum (mmHg)	Time (min)	Flow (mL/sec)	Notes
Pig 01 (control)	microjet	15	30	9	Partial CO_2 line failure in pig 03
Pig 02	aerosolization	15	30	9	
Pig 03	aerosolization	15	15	3	
Pig 04	aerosolization	15	15	3	

The surgical procedure was divided into four steps. The first step involved preparing the *in vivo* porcine model for video-assisted surgery. The anesthetized animals were positioned supine on the operating table with their paws and tail properly immobilized. The second step involved making a supraumbilical incision until the peritoneal cavity was opened. A Centryport multiport laparoscopic trocar was inserted using the Hasson technique. A 15-mmHg CO_2 pneumoperitoneum was inflated using a Striker laparoscopic insufflator following the usual procedure of classic videolaparoscopy. The third step involved using the multifunctional device for PIPAC (BhioQap sheath), and the following sequence of procedures was performed: 1. Ending insufflation and emptying the peritoneal cavity; 2. Opening the Centryport silicone sheath of the device; 3. Coupling the PIPAC sheath; 4. Checking the adequate locking of the two internal safety locks; 5. Inflating the cuff with 20 mL of PIPAC sheath air; 6. Coupling the plastic bell silicone sealant in the distal part of the PIPAC sheath; 7. Coupling the cannula of the Accutron CT-D contrast medium injector; 8. Creating a pneumoperitoneum with a Striker laparoscopic insufflator up to a pressure of 15 mmHg; 9. Positioning the 5-mm scope and checking the cavity; 10. Checking the insufflator display for pressure stability at 15 mmHg without change for 5 minutes; 11. Removing the surgical team; and 12. Administering the proposed solution (DIANEAL PD 1.5% Peritoneal Dialysis Solution, Baxter + 2% silver nitrate [100mL]) under pressure using the Accutron CT-D contrast medium injector. The 15-mmHg intraperitoneal pressure was maintained for 30 minutes in pigs 01 and 02 and for 15 minutes in pigs 03 and 04. After this period, the insufflator was switched off and the aerosolized content was suctioned using a suction probe with filter. The fourth step involved obtaining peritoneal biopsies. A conventional laparotomy was performed to obtain the biological material for anatomopathological examination. Samples were obtained from 11 previously chosen abdominal regions to represent drug distribution in the upper abdomen, mid abdomen, and lower abdomen (Figure 1). The specimens were obtained with cold biopsy forceps and immediately immersed in formalin for fixation.

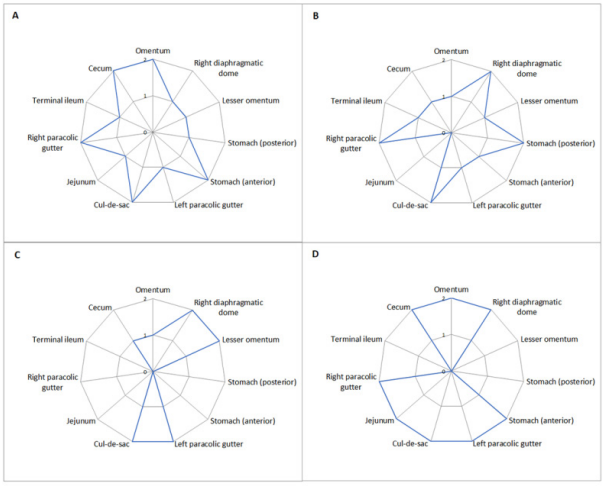

Figure 1 - A) Pig 01 (microjets for 30 min). **B**) Pig 02 (aerosolization for 30 min). **C**) Pig 03 (aerosolization for 15 min). **D**) Pig 04 (aerosolization for 15 min). Radial staining scale: 0- no staining, 1- weak staining, 2- moderate staining.

Histological analysis

All histological examinations were performed by our pathology department. Serial 3 to 4-µm-thick sections were cut from each specimen and stained with eosin for preparation of histological slides in order to measure the degree of silver salt uptake on the mesothelial surface of the tissue. Hematoxylin was not used to allow a better visualization of silver salt staining (dark shades) in the tissue, thus avoiding potential false positives. All slides were reviewed by the same team of pathologists. The degree of silver salt staining was assessed by simple (optical) microscopy and classified as

follows: (0) no staining – no silver salt staining was detected on the mesothelial surface; (1) weak staining – low expression of silver-stained spots, corresponding to a discontinuous (heterogeneous) monolayer covering at least 10% of the mesothelial surface; (2) moderate staining – intermediate expression of silver-stained spots, corresponding to a continuous (homogeneous) monolayer covering up to 80% of the mesothelial surface; and (3) strong staining – high expression of silver-stained spots, corresponding to a continuous (homogeneous) monolayer covering more than 80% of the mesothelial surface or evidence of the formation of salt aggregates in more than one layer.

■ Results

All animals were alive at the end of the experiment. None of the animals showed signs of hemodynamic instability throughout the procedure, especially during injection of the proposed substance. The total injected volume was 100 mL, and injection time ranged from 12 seconds in pigs 01 and 02 to 34 seconds in pigs 03 and 04. Although intra-abdominal pressure increased during injection, it did not exceed 20 mmHg in any of the animals. This increase in pressure was compensated by the insufflator itself.

In pig 01 (microjets, 9 mL/sec for 30 min), the samples obtained from all 11 abdominal regions showed evidence of silver nitrate, indicating that the substance was distributed throughout the peritoneal cavity. Silver nitrate staining was moderate in five regions (45.4%), while all other regions showed weak staining (Figure 1).

In pig 02 (aerosolization, 9 mL/sec for 30 min), only the jejunal sample did not stain with silver nitrate. The other 10 regions were positive for this marker. In four samples (36.3%), staining was rated as moderate (Figure 1).

In pig 03 (aerosolization, 3 mL/sec for 15 min), there was a leak in the CO_2 cannula, leading to a partial failure of aerosolization and solution leakage outside the cavity by reflux. In six abdominal regions, there was no evidence of silver nitrate staining. Of five regions showing silver nitrate staining, 36.3% had moderate staining (Figure 1).

In pig 04 (aerosolization, 3 mL/sec for 15 min), eight regions (72.7%) showed moderate silver nitrate staining (Figure 1).

■ Discussion

To our knowledge, this is the first study conducted in Brazil to explore the concept of aerosolization using a single-port device. The understanding of carcinomatosis as a chronic process of inflammation formation and development of neoplastic cells in different parts of the body gave rise to the concept of 'cell entrapment'[10]. In the context of cell entrapment, the procedure using a single-port device with the smallest diameter possible also explores the idea of reducing peritoneal violation, scar formation, and the need for secondary implant placement. This procedure was first described by Robella *et al.*[11]. It has the advantage of producing a single scar on the abdominal wall, thus avoiding technical difficulties in controlling the disease in future resections.

The traditional technique, if the trocars are maintained in the midline, can achieve a similar goal to that achieved with single-port devices. The experience of the surgical team, however, can be an important determinant in the choice of single-port or multiport devices. Perhaps the determining factor for choosing one or the other is the proper visualization of the procedure. The use of a 5-mm scope was not adequate for comfortable visualization of the four procedures performed in the present study. It is our impression that 10-mm

scopes may be more suitable for laparoscopic digestive and gynecological procedures, making the visualization of the procedure more comfortable for the surgical team. Therefore, the direct visualization of the application and the possibility of using 10-mm scopes may be essential to make the technique using a single-port device the preferred option for PIPAC.

The use of IPC to control carcinomatosis has been shown to be effective in settings such as ovarian cancer[12] and pseudomyxoma peritonei[13]. In recent years, response to the use of chemotherapy in the intraperitoneal cavity has been potentiated by different techniques, such as chemotherapy dose escalation, hyperthermia, pressure, and aerosolization[14]. Reymond *et al.*[6] applied the concept of breaking a liquid therapeutic substance into microdroplets for dispersal in the form of an aerosol for the treatment of carcinomatosis by PIPAC. The most important feature of this novel application process is aerosolization associated with pneumoperitoneum pressure. The therapeutic aerosol generated by this process assumes the behavior and distribution pattern of gases. The ability of gases to rapidly and homogeneously diffuse across the physical space improves the distribution of the therapeutic solution in the abdominal cavity. The depth of tissue penetration changes when the aerosolized liquid is associated with the CO_2 pressure of the videolaparoscopy[4]. The intraperitoneal pressure of the pneumoperitoneum modifies the 'peritoneal permeability' and the permeability of peritoneal metastases, doubling the concentration of the substance in the extracellular space and increasing fluid hydraulic conductivity by five times[15,16].

Our drug delivery system for multidirectional drug diffusion under direct visualization designed for the application of IPC in the laparoscopic setting aims to reproduce the concept applied by Reymond *et al.*[6] and minimize drug concentration near the application port. The homogeneous intra-abdominal drug distribution observed in the samples analyzed in the present study may provide some responses to criticisms found in the current literature regarding unidirectional devices[17]. In future studies, discussions of the importance of drug diffusion should encompass the understanding of the peritoneal circulation and stability of the 'therapeutic mist'. The peritoneal cavity is not a static environment, and maintaining the particles in suspension by reducing transitions back to a liquid form in the face of physical barriers seems to be a key factor. This allows the aerosol to remain suspended for a longer time under the effect of the pneumoperitoneum. Our mechanism of multidirectional aerosolization is able to maintain the aerosolized particles more dispersed by holding them in suspension for a longer time. The 'therapeutic mist' observed in bench tests of the device was successfully reproduced in the experiments described in the present study, demonstrating a trend toward stability of the aerosolization produced by the multidirectional device.

In the four porcine models analyzed in the present study, however, there was no pattern of drug distribution. Total duration of exposure seems to be the most significant factor for a more effective drug distribution, whether using microjets or aerosolization. In the two animals exposed to 30 minutes of PIPAC, only one abdominal region did not come into contact with silver nitrate. In the two animals exposed to 15 minutes of PIPAC, up to eight regions were not stained with silver nitrate, but without an identifiable pattern of drug distribution.

The aerosolization process analyzed by Göhler *et al.*[18] showed that aerosol formation was only effective at a flow rate greater than 25 mL/min. The flow rate used in our porcine models was greater than that and was potentiated by the flow of compressed air. Our choice of using higher flow rates was based

on the results of bench tests performed to validate the BhioQap equipment, in which we identified two different flow rates suitable for application to our models. When analyzing the two proposed procedures, using 9 mL/sec or 3 mL/sec, the lower flow rate made the process more stable with a pneumoperitoneum variation small enough to be compensated by the laparoscopic insufflator. This leads us to believe that, as demonstrated by Göhler *et al.*[18], the use of flow rates below the proposed threshold of 30 mL/min produces an aerosolization process that is more suitable for the equipment used in the laparoscopic environment.

The method of PIPAC application associated with videolaparoscopy described in the present study has the advantage of being a minimally invasive treatment for patients previously considered candidates only for more aggressive treatments, such as cytoreductive surgery and hyperthermic chemotherapy. The role of PIPAC in the treatment of peritoneal carcinomatosis has yet to be fully defined. However, by combining advantages of video-assisted surgery, such as the versatility and low morbidity of the procedure, with those of IPC application, PIPAC becomes an important alternative when planning the treatment of peritoneal carcinomatosis. The four procedures described in the present study proved to be safe and easy to perform by laparoscopically experienced surgical teams. The processes described in the present study can serve as a guide for surgeons seeking to perform this procedure safely.

■ Conclusions

PIPAC was applied using a novel single-port device capable of performing the whole procedure with multidirectional application of the therapeutic substance under direct visualization. This approach proved to be feasible and safe in its first use in an *in vivo* animal model in Brazil. The pattern of drug distribution was broad, with the presence of silver nitrate in most abdominal regions, especially in animals exposed to the drug for 30 minutes. Based on this finding, we can conclude that the duration of exposure is essential for good drug distribution. Our sample of only four animals was not large enough to demonstrate an association between aerosolization and a higher concentration of silver nitrate solution in the stained abdominal regions.

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