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Comparing Distribuition and Droplet size of Ultrasonic Aerosolization with Traditional Pipac of Therapeutic Substance in Porcine Models

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Abstract

Background: The characteristics of peritoneal metastases explain the resistance in the action of systemic chemotherapeutic agents. PIPAC (Pressurized Intraperitoneal Aerosol Chemotherapy) optimizes the distribution and penetration depth of chemotherapeutics. Ultrasonic PIPAC brings features that are still unexplored in traditional PIPAC. This paper aims to evaluate the particle distribution of the ultrasonic tool in PIPAC.

Material and Methods: Avaliação da distribuição da aerossolização ultrassônica de solução de nitrato de prata no espaço peritoneal de 5 modelos porcinos por biópsias peritoneais. A descrição das características do aerossol ultrassônico formado e a análise peritoneal das amostras patológicas foram comparadas com 5 modelos de aerossolização por alta pressão realizados em artigo publicado anteriormente.

Droplet size measurement was performed at three percentiles of ultrasonic aerosol formed from two aerosol rod designs and compared with mechanical aerosolization. Moreover, the tissue distribution was observed and compared by pathology. We described the physical characteristics of ultrasonic aerosolization in 5 laparoscopic procedures (porcine models).

Results: The mean ultrasound aerosolization time was 38.1 minutes with maximum temperature of 39°C. The medium of ultrasonic aerosolizations dropless creat was 39,17µm and the hat tip had an average of 33.10µm. We also notice that the droplet size was better at ultrasonic devices (hat and multidirectional), and beyond that, the upper abdomen drug distribution was superior for multidirectional US devices than standart PIPAC.

Conclusions: Ultrasonic aerosolization is feasible with adequate droplet size and the possibility of heating as well as maximize the aerosolization time. But ultrasonic aerosolization also seems to have a better distribution when compared to traditional PIPAC technology.

Keywords: Drug delivery; Peritoneal metastasis; Intraperitoneal chemotherapy; Hyperthermia; Medical devices

Introduction

The peritoneal surface has always been a challenge that needs to be overcome in cancer treatment. Unlike metastases resulting from hematogenous or lymphatic dissemination, peritoneal metastases are implanted directly in the peritoneum through the “cell entrapment” mechanism - it demonstrate resistance to the action of systemic chemotherapeutics and the difficult for therapeutic substances to penetrate the peritoneal carcinomatosis tissue [1,2].

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The use of chemotherapy directly in the peritoneal space proved to be a new way of delivering therapeutic agents [3]. In this context, different ways to enhance the action of therapeutic substances in the peritoneal space have been explored: modalities such as Hyperthermic intraperitoneal chemotherapy (HIPEC), [5] Early Postoperative Intraperitoneal Chemotherapy (EPIC), Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS), [6] and Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) [7] aims to increase the effectiveness of chemotherapeutic agents in the peritoneal space.

PIPAC, in particular, seeks to better explore both the distribution and depth of penetration of therapeutic agents into the peritoneal space [18]. It's rationale is manifold: using an aerosol rather than a liquid solution, PIPAC improves the homogeneity of spatial drug distribution; by applying artifcial hydrostatic pressure to the abdomen, PIPAC enhances drug penetration into the tumoral tissue [19] Also, repeated PIPAC cycles are possible, which is a precondition for effective palliative chemotherapy, it's main use [20]. Finally, comparing tumor biopsies between PIPAC cycles allows histological assessment of tumor response [21].

Several studies suggest further technological development is needed to explore PIPAC's full therapeutic potential. A possible opportunity is to use aerosol ultrasound generators, standard method in pulmonary medicine [17]. The usPIPAC technology has several advantages: no gas fow is needed during the application, the small size of the trump allows minimally invasive use, the fow of 0.1 ml/s allows aerosolization of larger volumes of therapeutic solutions, the technology can aerosolize aqueous or oily substances, and the device can be controlled remotely [18].

This study evaluated the potential use of ultrasound technology to improve PIPAC's performance at abdominal surface field. We tested the feasibility of usPIPAC compared its performance with the available traditional comparator - and registered the physical properties that could enhance PIPAC usual characteristics in porcine laparoscopic models with usPIPAC. In this article we aim to elucidate how the distribution of usPIPAC can enhance the usual technology.

Material and Methods

Particle size measurement

The analysis of the size of the therapeutic cloud droplet formed by the ultrasonic aerosol was measured in 6 different aerosolizing tips using an ultrasonic aerosolization generator with patent PCT/BR2020/000015. Ultrasonic tips were divided by aerosolization rod design - hat shape and multidirectional shape. The aerosolizing therapeutic cloud was evaluated at 4 different moments. Four different measurements of traditional ultrasonic aerosolization with equipment approved in Brazil by ANVISA served as a comparative parameter for measuring the size of the therapeutic cloud droplet formed by traditional aerosolization. Analysis was performed in Campinas on March 2021 and June 2021 at T&E Analitica - Analytical and Scientific Center - Measurements were obtained using the equipment "Malvern Panalytical's Spraytec" (serial number-MAL1056092) with 300 mm lenses for water. Aerosol droplet size measurements were performed in micrometers (µm) and the percentiles 10(V-10), 50(V-50) e 90(V-90) were analyzed.

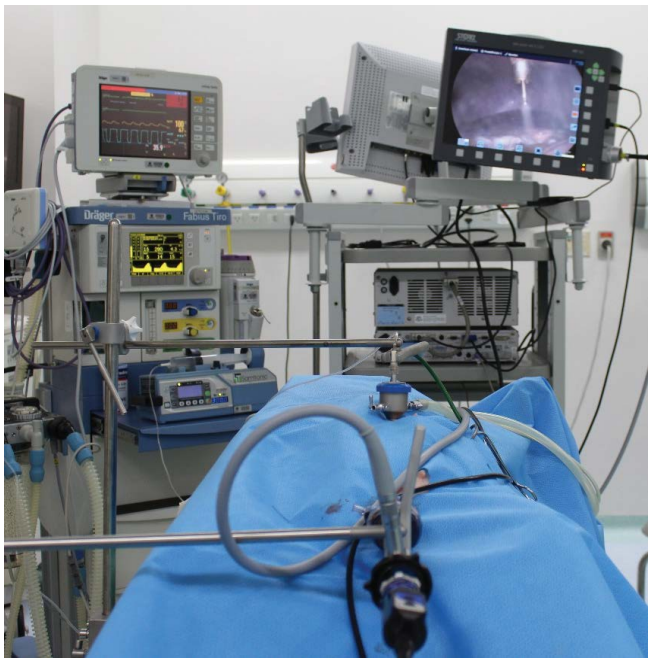

Figure 1: Animal model in aerosolization.

Aerosolization in animal models and ethical aspects

Five procedures were performed in random porcine models in the premises of the Experimentation and Surgery Training Center (CETEC) of the Research Institute of the Hospital Israelita Albert Einstein São Paulo-Brazil. The procedures were approved by the animal research ethics committee - no. 4490-20. All procedures followed the ethical principles established by the Brazilian Society for Laboratory Animal Science (SBCAL/COBEA). The animals underwent laparoscopy technique with pneumoperitoneum at 8 mmHg. They received general anesthesia conducted throughout the procedure by the laboratory's veterinarian.

The ultrasonic device was attached to a trocar and fixed in a mechanical arm, as shown in figure 2. They were submitted to ultrasonic aerosolization with 200 ml silver nitrate, 2%. The solution volume used was injected with minimum pressure (<5 PSI) via a 50 ml syringe device (Santronic ST 6000) changed sequentially until reaching a volume of 200 ml. Esophageal thermometers were positioned inside the peritoneal cavity.

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After aerosolization, the pneumoperitoneum was kept for 20 minutes to promote the deposition of the therapeutic mist. After that, the animals underwent laparotomy and biopsies were performed for histopathological analysis. Samples were obtained from the upper abdomen (right diaphragm, left diaphragm, lesser omentum, anterior stomach and lower stomach), middle abdomen (right gut, omentum, jejunum, ileum and left gut) and lower abdomen (right iliac fossa, bladder wall, cul-de-sac and left iliac fossa).

Pathological assessment of peritoneal distribution

The distribution of the therapeutic cloud in porcine models using ultrasonic energy was evaluated using the same methodology published at previous articles: A prototype single-port device for pressurized intraperitoneal aerosol chemotherapy. Technical feasibility and local drug distribution; Seitenfus R, et al. Acta Cir Bras. 2017 Dec;32(12):1056-1063. doi: 10.1590/s0102-865020170120000007. PMID: 29319734. and Assessment of the aerosol distribution pattern of a single-port device for intraperitoneal administration of therapeutic substances. Surg Endosc. 2019 Oct;33(10):3503-3510. doi: 10.1007/s00464-019-07043-y. Epub 2019 Aug 1. PMID: 31372889. Seitenfus R, et al.

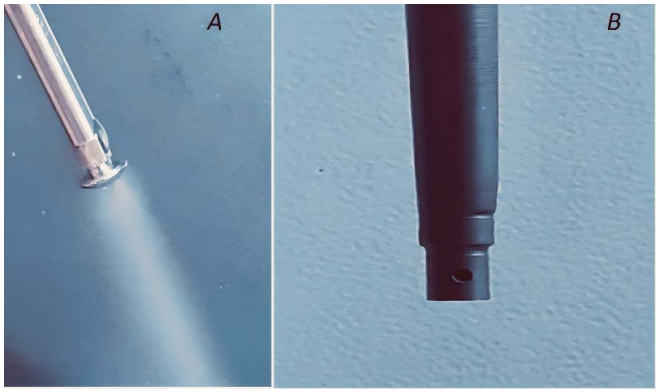

Figure 2: A- hat tip B- multidirectional tip

The methodology evaluates the surface distribution and impregnation of silver nitrate through the analysis of anatomopathological samples obtained in different regions of interest in the upper, middle and lower abdomen. 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. The animal tests were carried out by the same team that performed the aerosolization procedure, sample collection and final analysis of the pathology, which made it possible to use the database collected in work published in the year 2019 as a standard for comparing distribution of both methods in porcine models.

Statistical analysis

Analysis of droplet size measured of the formed therapeutic cloud was extracted from the report produced by the equipment used in particle measurement and arranged in an Excel spreadsheet. The means were gathered in 4 groups: Standard PIPAC, hat tip ultrasound, titanium multidirectional ultrasound and aluminum multidirectional ultrasound. These values were then presented as means and their respective standard deviations. Comparison of means was performed through the Analysis of Variance (ANOVA) followed by the Games-Howell post hoc test for multiple comparisons. Means with standard deviation and their respective 95% confidence interval were presented. The analyses were carried out by the WINPEPI 11.65 program (Abramson, J.H. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. Epidemiologic Perspectives & Innovations 2011, 8:1).

The distribution in the different regions in the animal models was entered into the Excel program and subsequently exported to the SPSS v program. 20.0 for statistical analysis. The intensities between categories were compared using the Mann Whitney test and between three or more categories using the Kruskal Wallis test. A significance level of 5% was considered for the comparisons established.

Results

Size of the droplet

The total number of aerosolized droplets measured was 56 649, an average of 9441 aerosolized droplets per measurement. The maximum droplet size found in all ultrasonic aerosolizations was 638 µm in the multidirectional design. The smallest droplet size with a significant volume was 11.6 µm in the cap design tip. The total volume of aerosolized droplets with a size below 54 µm varied according to design and material used: hat tip (83.7% - 89.6%), titanium multidirectional tip (68% - 70.9%) and aluminum multidirectional tip (65.7% - 69.3%). The V50 mean of all ultrasonic aerosolizations was 39,17 µm. The comparison analysis was made in 3 different volume ranges in the percentiles 10(V-10), 50(V-50) and 90(V-90).

In the V-10 range, the standard had an average of 29.47 µm (95% CI: 26.62 to 32.32), the hat tip an average of 18.78 µm (95% CI: 16.83 to 20.73), the titanium multidirectional

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an average of 23.05 µm (95% CI: 20.17 to 25.93), and the aluminum multidirectional an average of 22.16 µm (95% CI: 18.21 to 26.11). We found that hat rod ultrasonic aerosolization and the titanium or aluminum multidirectional aerosolization showed a significant difference in comparison with traditional aerosolization (P<0.01). When comparing the various forms of ultrasonic aerosolization, a significant difference (P<0.05) was shown in the comparison between the hat rod and the titanium multidirectional rod. There was no significant difference between the titanium multidirectional rod and the aluminum multidirectional, or the aluminum multidirectional rod and the hat rod (Graph 1).

In the V-50 range, the standard had an average of 48.70µm (95% CI: 45.96 to 51.44), the hat tip an average of 33.10 µm (95% CI: 28.34 to 37.86), the titanium multidirectional an average of 41.95 µm (95% CI: 36.79 to 47.11), and the aluminum multidirectional an average of 42.48 µm (95% CI: 35.10 to 49.86). Ultrasonic aerosolization showed statistical difference when compared to the standard aerosolization pattern in the hat rod aerosolization (48.70 µm vs 33.10 µm = P<0.01) and in the titanium aerosolization rod (48.70 µm vs 41.95 µm = P<0.05). Among the ultrasonic aerosolizations, statistical significance was identified between the hat rod and both titanium and aluminum multidirectional rods (33.10 µm vs 41.95 µm = P<0.05) (33.10 µm vs 42.48 µm = P<0.05). There was no significant difference when comparing titanium multidirectional rods with aluminum multidirectional rods in the V-50 range. (Figure 3)

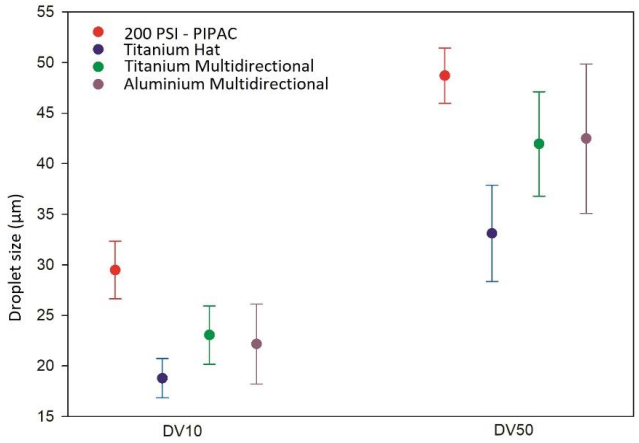

Figure 3: Graphic representation of the Ultrasonic Aerosolized Droplet Size Distribution in V10 and V50.

The V-90 assessment showed no significant difference between the groups. In the V-90 range, the standard had an average of 77.85µm (95% CI: 45.76 to 109.94), the hat tip an average of 57.98 µm (95% CI: 39.86 to 76.10), the titanium multidirectional an average of 80.81 µm (95% CI: 47.27 to 114.35), and the aluminum multidirectional an average of 84.52 µm (95% CI: 42.33 to 126.71).

We know that the ideal size average determined by today's standard of traditional PIPAC 25 µm - 45 µm. If we compare our percentile, we can notice that USPIPAC will have a greater number of droplets of adequate size in its whole procedure [7].

Animal distribution differences (usPIPAC x standard)

In animal model applications, 5 ultrasonic aerosolization procedures were simulated (video-1). Procedures were initially planned for 6 animals, however, the ultrasonic transducer of the prototype heated up and aerosolization failed, making it impossible to carry out the 6th procedure and stopping the aerosolization of the entire solution proposed in the 5th animal model. Subsequently, a break in the electrical wire that feeds the aerosolizing rod was identified. The mean aerosolization time was 38.1 minutes, including the injection pump syringe change (3 changes). The temperature after 30 minutes of aerosolization ranged from 3 to 5 degrees Celsius (°C) and did not exceed 39°C. All models showed stability in the pneumoperitoneum observed in the videolaparoscopy insufflator (Table 1).

Data from 5 models with the traditional PIPAC, 3 with the hat and 2 with the Multidirectional were analyzed. The median considering all animals and locations in the upper abdomen was 1 (range of 0-3) for the traditional PIPAC, 0 (range of 0-3) for the Hat and 2 (range of 0-3) for the Multidirectional with statistically significant difference between the Hat and Multidirectional devices (p=0.042) The median scores found in the upper abdomen in each animal and their respective ranges are presented in table 1. There was a statistically significant difference in intensity in model 5, with greater dyeing distribution in the traditional PIPAC than in the hat (p=0.032). Also when comparing the models within the multidirectional device, there was greater distribution in model 4 when compared to model 1 (p=0.009).

The median considering all animals and locations in the mid-abdomen was 3 (range 0-3) for the traditional PIPAC, 2 (range 0-3) for the hat and 2.5 (range 0-3) for the Multidirectional, with no statistically significant difference between the devices (p=0.793)

The median scores found in the middle abdomen in each animal and their respective ranges are presented in table 2. There was no statistically significant difference between the devices for mid-abdomen.

The median considering all animals in the lower abdomen was 3 (range 0-3) for the traditional PIPAC, 0.5 (range 0-3) for the hat and 0.5 (range 0-3) for the Multidirectional, with no statistically significant difference between the devices (p=0.192) The median scores found in the lower abdomen in each animal and their respective ranges are presented in table 3. There were no statistically significant differences between the devices for lower abdomen

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Table 1: Median (minimum-maximum) score for each type of device in the upper abdomen.

	Traditional PIPAC	Hat	Multidirectional	*p**
Model 1	0 (0-3)	0 (0-2)		0,548
Model 2	0 (0-3)		1 (0-2)	0,548
Model 3	0 (0-3)	0 (0-3)		1,000
Model 4	2 (0-3)		3 (2-3)	0,222
Model 5	3 (1-3)	1 (0-2)		**0,032**
*p***	0,174	0,623	**0,009**	

*Mann Whitney test ** Kruskal Wallis test

Table 2: Average particle size (V-percentile, σ-standard deviation and µm-micrometers).

	V – 10(σ) (µm)	V -50(σ) (µm)	V – 90(σ) (µm)	Aerosolizing rod material	Total number of measured samples
200 PSI- parameter	29.47 (1.79)	48.70 (1.72)	77.85 (20.17)	X	10402
Hat	19.54 (2.03)	34.78 (5.19)	61.39 (11.29)	Titanium	7278
Hat	18.01 (1.38)	31.42 (2.99)	54.57 (19.79)	Titanium	5842
Multidirectional	22.35 (2.88)	42.03 (5.38)	85.4 (33.76)	Titanium	10277
Multidirectional	23.74 (2.19)	41.86 (3.63)	76.21 (25.56)	Titanium	2403
Multidirectional	22.04 (3.05)	41.79 (6.02)	80.22 (38.25)	Aluminum	10450
Multidirectional	22.27 (3.92)	43.16 (7.16)	88.82 (36.73)	Aluminum	9997

*teste de Mann Whitney **teste de Kruskal Wallis

Table 3: Median (minimum-maximum) score for each type of device in the lower abdomen.

	Traditional PIPAC	Hat	Multidirectional	*p**
Model1	3 (3-3)	1 (0-3)		0,114
Model 2	1,5 (0-3)		0,5 (0-1)	0,686
Model 3	1,5 (0-3)	0 (0-1)		0,486
Model 4	3 (0-3)		1 (0-3)	0,343
Model 5	0 (0-3)	0,5 (0-3)		0,686
*p***	0,273	0,373	0,536	

*teste de Mann Whitney **teste de Kruskal Wallis

Discussion

Aerosol delivery of a therapeutic substance has been used in the treatment of lung diseases and is benefic due to its direct action on the target tissue, limited systemic absorption, and reduced side effects [7]. These principles are also observed in the peritoneal space. The understanding of the natural history of peritoneal carcinomatosis as a local presentation of a stage IV systemic disease drew attention to the possibility of using the peritoneal space as a route for administering therapeutic substances for the control of neoplasms.

New ways of delivering therapeutic substances in the peritoneal space seek to increase their effect on peritoneal metastases. Direct aerosolization into the peritoneal space seems to improve both drug distribution and penetration [8,9]. The delivery of chemotherapy in the form of aerosolized therapeutic mist into the peritoneal space was first described in 2000 by Reymond et al. (PIPAC- Pressurized Intraperitoneal Aerosol Chemotherapy) [10]. In this application method, aerosolization is carried out through a mechanical high pressure microinjection system. The median droplet size formed in this kind of aerosolization is 25 µm with a range of 0.5-875 µm. Sande et al. [11] found changes in the mean particle size when the infusion rate and pressure in the

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system were changed. At the infusion speed of 0.5 ml/s with a pressure of 20 bar, they were able to identify drops formed in 50% of the (V-50) 47(±2) µm sample. This value changes when the flow is maintained, but the pressure decreases to 5 bar, changing the V-50 - 51(±1) µm. Injection flow is most closely related to particle size in the microinjection system. When using an injection of 0.8 ml/s and a pressure of 20 bar, the particle size changes significantly with V-50 30(±3) µm [12].

The ultrasonic aerosolization used here performs aerosolization at low pressure levels. This is because, unlike the traditional form of PIPAC, the pressure applied is minimal and only controls the flow of the therapeutic substance that crosses the rod responsible for aerosolization. The aerosolization mechanism is based on the principle of ultrasonic cavitation of the liquid that reaches the tip of the aerosolizing rod. The aerosolization method occurs as soon as the device is activated without the latency observed in micropump injection aerosolization processes, optimizing the time of surgery and therapeutic fog.

The particles aerosolized by ultrasound have a droplet size not smaller than those achieved through aerosolizations by microinjection pumps. The V-50 mean obtained in all ultrasonic aerosolization samples was 39.17 µm, reaching 33.10 µm when assessing the aerosolizing rod with a hat tip in an exclusive way. The major difference between the two processes is in the formation of a therapeutic mist with a narrower particle range. In ultrasound aerosolization, 65.7% to 89.6% of aerosol droplets are close to the ideal size found in the traditional pressure aerosolization method. This may be an advantage of ultrasonic aerosolization when compared to traditional PIPAC, as we will have a greater number of droplets of adequate size than the average determined by today's standard of traditional PIPAC 25 µm - 45 µm [7]. By expanding this analysis by droplet size range produced, we found a higher production of smaller ultrasonic aerosolized droplets in V-10 ranges ((29.47 µm Standard : vs 18.78 µm Hat ($P<0.01$), 23.05 µm Titanium multidirectional ($P<0.01$) and 22.16 µm Aluminum multidirectional ($P<0.01$)) and V-50 ((48.70 µm Standard: vs 33.10 µm Hat ($P < 0.01$) and 41.95 µm Titanium multidirectional ($P<0.05$)). Although the V-50 mean of the aluminum multidirectional rod is lower than the mean in standard aerosolization (48.70 µm x 42.48 µm), statistical significance was not reached after adjustment for multiple comparisons. Comparison analyzes of aerosol formation by ultrasound allow to identify that ultrasonic energy produces particles 12.7% to 33% smaller than the established standard. How much this gain, both in the smaller size of the formed aerosol and in the volume of aerosol droplets within the ideal V-50, for a narrower droplet size range, can represent a benefit in the action of therapeutic agents in the peritoneal space is a matter which will have to be explored in future work.

This ultrasonic aerosolization feature may be explored as a way to enhance the effect of chemotherapy in the peritoneal space in future observations.

We know for now that usPIPAC much lower injection flows and pressure, originate a lower particle kinetics than those observed in microinjection pump aerosolization with pressures that can reach up to 20 bar. This can negatively influence the distribution in the peritoneal space. So we also did initial observations obtained here in the animal models. It lead us to believe that the final design of the aerosolizing rod is remarkable to minimize this possible difficulty in the distribution by ultrasonic aerosolization. We notice that the ultrasonic devices perform better than standard device for upper abdomen surface, with statistical significance. That suggest that the distribution is better for ultrasonic device.

Conclusion

Ultrasonic aerosolization proved to be possible in animal models, bringing evident differences in the formed therapeutic mist. The size of the ultrasonic droplet formed is suitable for the pattern identified in the aerosolization equipment by injection, adding to the ultrasonic therapeutic mist promising features such as: heating of the therapeutic agent, longer aerosolization time and greater volume of droplets close to the ideal droplet size. Further preclinical and clinical comparative studies are needed to determine which aerosolizing technology is best suitable for PIPAC. Also usPIPAC at the form of multidirectional hat seems to have a better distribution compared to standard procedure.

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