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Pressurized IntraPeritoneal Aerosol Chemotherapy with one minute of electrostatic precipitation (ePIPAC) is feasible, but the histological tumor response in peritoneal metastasis is insufficient

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**Short title:** One minute ePIPAC

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Summary

Introduction

Electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC) has shown superior penetration depth and tissue uptake compared to standard PIPAC. We investigated the feasibility and objective tumor response to ePIPAC with one minute of precipitation in patients with peritoneal metastasis (PM).

Materials and Methods

Patients with PM from various abdominal cancers were included in an amendment to the ongoing prospective PIPAC-OPC2 trial. Colorectal and appendiceal PM were treated with oxaliplatin, patients with PM from other primaries were treated with a combination of cisplatin and doxorubicin. Three ePIPAC procedures were planned in each patient including repeated peritoneal biopsies for response evaluation. After emission to the peritoneal cavity, the aerosolized chemotherapeutics were precipitated for one minute followed by immediate exsufflation and abdominal closure. Histological regression from the first to the third ePIPAC was evaluated according to the Peritoneal Regression Grading Score (PRGS) and compared to data from the PIPAC-OPC1 trial. Complications and toxicities were recorded according to Dindo-Clavien and CTCAE.

Results

Sixty-five ePIPAC procedures were performed in 33 patients (median 2, range 1-6). Ten patients were eligible for response evaluation based on biopsies from the first and third ePIPAC procedure. Four patients had disease progression, four patients had regressive disease, and two patients had stable disease according to PRGS. No life threatening adverse reactions and no mortality was observed following ePIPAC.

Conclusion

One minute ePIPAC was feasible and safe, but the histological tumor response was insufficient compared to standard PIPAC directed therapy with 30 minutes passive diffusion time.

Key words: PIPAC; ePIPAC; peritoneal metastasis; feasibility; tumor response; intraperitoneal chemotherapy.
Abbreviations:
ePIPAC: Electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy

PIPAC: Pressurized IntraPeritoneal Aerosol Chemotherapy

PM: Peritoneal metastasis

PRGS: Peritoneal Regression Grading Score
1.0 Introduction

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is a safe and feasible treatment option in patients with peritoneal metastasis (PM) of gastrointestinal and gynecological origin [1-3]. PIPAC directed therapy may induce objective tumor response, stabilize or improve the patients’ quality of life and prolong survival in selected patients [1, 2, 4]. During a standard PIPAC procedure, the chemotherapy is nebulized within the peritoneal cavity and a steady state is maintained for 30 minutes [5, 6]. Compared to instillation of intraperitoneal chemotherapy by simple peritoneal lavage in an ex vivo model, the penetration depth and tumor tissue uptake of PIPAC directed chemotherapy seem superior [7], but especially in bulky disease, new techniques are needed to increase the exposure of cancer cells to chemotherapy. The CE certified Ultravision™ generator (Ultravision™, Alesi Surgical Ltd., UK) is used in standard laparoscopic procedures to clear smoke by means of electrostatic precipitation, which might also be used to charge the therapeutic aerosol in PIPAC directed treatment. By combining PIPAC and electrostatic precipitation (ePIPAC), the tissue uptake of two tracer substances was elevated up to tenfold and the visual field cleared after 15 seconds of electrostatic precipitation as opposed to the 30 minutes diffusion time in a standard PIPAC procedure [8]. The first in-human application in three patients found ePIPAC with 30 minutes of diffusion and electrostatic precipitation technically feasible, well tolerated and able to induce an objective tumor response [9]. However, based on data from an ongoing large animal model, ePIPAC with six minutes of diffusion and electrostatic precipitation might suffice (data presented at the Fifth International PIPAC Symposium 2018, Paris, France). Further, the gain of six minutes compared to one minute seemed minimal. Thus, ePIPAC with one minute of diffusion and electrostatic precipitation might offer the optimal treatment response with shortest possible time for surgery and anaesthesia. In this prospective study, we investigated if ePIPAC, with one minute of diffusion and electrostatic precipitation induced a similar or better histological tumor response compared to data from the prospective PIPAC-OPC1 study [4], where patients had standard PIPAC with 30 minutes of simple diffusion. Secondary, we evaluated if ePIPAC was comparable to standard PIPAC in terms of feasibility and patient safety.
2.0 Material and Methods

The patients in this study were recruited through an amendment to the PIPAC-OPC2 study, which is an ongoing ICH-GCP monitored prospective phase two study of patients with radiological, cytological or histological proven PM from gastrointestinal, ovarian or primary peritoneal cancer [10]. Patients were included through the interdisciplin ary tumor board meeting and had to be adults with an Eastern Cooperative Oncology Group performance status of less than 2. Eligible patients had a non-obstructed gastrointestinal tract and a maximum of one extraperitoneal metastasis. Women should be post-menopausal. Patients were excluded if they had a history of allergic reactions to doxorubicin or platinum, renal impairment (GFR < 40 ml/min), myocardial insufficiency (NYHA class > 2), impaired liver function (bilirubin >1.5 upper normal limit) or inadequate hematological function (ANC < 1.5 x 10⁹/L or plates < 100 x 10⁹/L).

2.1 ePIPAC

The standard PIPAC procedure has been described previously [4, 6, 11]. The same steps regarding safety and chemotherapy administration were followed during ePIPAC and a brush electrode (Ionwand™, Alesi Surgical Ltd., UK) was placed through the abdominal wall within the visual field of surgery (Figure 1). After intraperitoneal delivery of chemotherapy, the Ultravision™ generator was activated and applied a low current to the Ionwand™. The Ionwand™ emitted electrons and formed negative gas ions that collided with the aerosolized chemotherapy particles. Through the weak positive charge from the standard return electrode, the negatively charged aerosol particles were accelerated towards the peritoneum. The droplets were precipitated for at least one minute (or until the aerosol was cleared completely by visual inspection). Then, the abdomen was exsufflated and closed according to standard practice after PIPAC. Similar to PIPAC with 30 minutes diffusion time, the ePIPAC directed treatment was planned in a series of three procedures at intervals of four to six weeks. Patients with colorectal PM were treated with oxaliplatin 92 mg/m² body surface area (BSA), while patients with PM from other primary tumors were treated with cisplatin 7.5 mg/m² BSA and doxorubicin 1.5 mg/m² BSA.

Procedure related bleeding, bowel perforation or postprocedural intraperitoneal abscess were defined as surgical complications and recorded according to Dindo-Clavien [12]. The remaining 30
days toxicity or adverse events rate was documented according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) [13].

**Figure 1.**

### 2.2 Objective tumor response

The peritoneal biopsies and peritoneal lavage fluid were retrieved and processed as described previously [4]. In short, ascites or peritoneal lavage fluid was analysed by conventional cytology augmented by immunocytochemistry at the discretion of the dedicated cytopathologist. The results were positive if either malignant or suspicious cells were found. Three or four punch biopsies from the peritoneum were retrieved before each ePIPAC procedure (if possible), and the biopsy sites were marked by clips to ensure subsequent biopsies from the same area. The histological regression was evaluated by the four-tied Peritoneal Regression Grading Score (PRGS) [14]. The PRGS distinguishes between four grades of tumor regression depending on the ratio between regressive changes and the presence of vital cancer cells or classical necrosis. PRGS 1 (complete response) is defined as no tumor cells and only regressive changes present; PRGS 2 (major response) is regressive changes predominant over tumor cells; PRGS 3 (minor response) is predominance of tumor cells, but regressive changes present, and PRGS 4 (no response) is no regressive changes and only tumor present [4]. As multiple biopsies are analysed, the mean PRGS should be presented [14].

### 2.3 Statistics

Data from the prospective PIPAC-OPC1 study showed that the risk of progression was 11%, when based on PRGS scores before the first and third PIPAC procedure in patients with PM of different origin [4]. The patient inclusion was planned in small groups to ensure that ePIPAC did not lead to more patients with progression using the same response criteria as the PIPAC-OPC1 study. The number of patients with progression was calculated after completion of three PIPAC procedures in five, ten and twenty patients. Based on a binominal distribution and expected risk of 0.11, the limits for terminating the study were 1) five patients included and ≥ two with progression (p=0.01), 2) ten
patients included and ≥ three with progression (p=0.02) or 3) twenty patients included and ≥ five with progression (p=0.02). P-values were two-tailed and a p-value of 0.05 was considered statistically significant. The statistical software Stata, version 13 (Stata Corp, Texas, USA) was used for statistical analyses.

2.4 Ethics and trial registration

This study was conducted according to a predefined protocol and the Declaration of Helsinki, and monitored according to the ICH-GCP recommendations. The PIPAC-OPC2 protocol was approved by the Regional Scientific Ethical Committees for Southern Denmark (S-20160100) and the Danish Medicines Agency (2016083464). The amendment on ePIPAC was approved by the ethical committee in April 2018. Oral and written consent from participants were mandatory. ClinicalTrials.gov identifier NCT03287375, European Clinical Trials Database (EudraCT) number 2016-003394-18.
3.0 Results

The patients were included from April 2018 to April 2019 (Table 1). Sixty-five ePIPAC procedures were performed in 33 patients (median 2 ePIPACs, range 1-6) (Figure 2). Three patients were excluded due to non-access to the peritoneal cavity at the first ePIPAC procedure. Two patients died more than one month after the first ePIPAC procedure, and no causalities to the ePIPAC were suspected. Four patients continued standard PIPAC after their first treatment due to the findings of the interim analysis, thus excluded from ePIPAC response evaluation. Two patients were excluded due to protocol violations: One patient had potentially resectable metastases and was not biopsied throughout the course of therapy, and one patient did not follow the treatment intervals between ePIPAC two and three. Thus, ten patients were eligible for response evaluation based on biopsies from the first and third ePIPAC procedure (Table 2 and 3). According to the PRGS, four patients had disease progression, four patients had regressive disease, and two patients had stable disease. Three patients converted to positive cytology from the first to the third ePIPAC procedure, two patients converted to negative cytology, and five patients remained unchanged. ePIPAC was repeatable in most patients and no Dindo-Clavien grade 2-5 occurred. The median operative time of the first ePIPAC procedure was 67 minutes (range 32-110). Five severe adverse reactions in three different patients were documented (in-hospital treatment of bowel obstruction and pain), but no life threatening adverse reactions and no mortality was observed (Table 4).

Figure 2.
Table 1. Baseline characteristics of patients who were treated with electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>33</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>59 (31-73)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/23</td>
</tr>
<tr>
<td>Previous systemic chemotherapy</td>
<td>32</td>
</tr>
<tr>
<td>Bi-directional treatment*</td>
<td>12</td>
</tr>
<tr>
<td>Primary tumor origin</td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>1</td>
</tr>
<tr>
<td>Stomach</td>
<td>8</td>
</tr>
<tr>
<td>Small bowel</td>
<td>3</td>
</tr>
<tr>
<td>Bile duct</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
</tr>
<tr>
<td>Appendix</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal</td>
<td>5</td>
</tr>
<tr>
<td>Ovary</td>
<td>10</td>
</tr>
<tr>
<td>Uterus</td>
<td>1</td>
</tr>
<tr>
<td>Primary tumor resected</td>
<td>15</td>
</tr>
<tr>
<td>Extraperitoneal metastasis</td>
<td>5</td>
</tr>
</tbody>
</table>

* Systemic chemotherapy in between each ePIPAC
Table 2. Baseline characteristics of ten patients who received three series of electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Tumor origin</th>
<th>Primary tumor resected</th>
<th>Baseline PCI</th>
<th>ePIPAC OX or C/D</th>
<th>Bi-directional chemotherapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>F</td>
<td>Ovary</td>
<td>No</td>
<td>21</td>
<td>C/D</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>M</td>
<td>Colorectal</td>
<td>Yes</td>
<td>2</td>
<td>OX</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>Gastric</td>
<td>No</td>
<td>2</td>
<td>C/D</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>F</td>
<td>Colorectal</td>
<td>No</td>
<td>1</td>
<td>OX</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>F</td>
<td>Gastric</td>
<td>Yes</td>
<td>8</td>
<td>C/D</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>M</td>
<td>Colorectal</td>
<td>No</td>
<td>22</td>
<td>OX</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>Appendiceal</td>
<td>No</td>
<td>13</td>
<td>OX</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>F</td>
<td>Gastric</td>
<td>No</td>
<td>3</td>
<td>C/D</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>M</td>
<td>Small bowel</td>
<td>Yes</td>
<td>10</td>
<td>C/D</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>F</td>
<td>Bile duct</td>
<td>No</td>
<td>4</td>
<td>C/D</td>
<td>No</td>
</tr>
</tbody>
</table>

C/D: cisplatin/doxorubicin, F: female, M: male, OX: oxaliplatin, PCI: Peritoneal Cancer Index

*Systemic chemotherapy in between each ePIPAC
Table 3. Objective tumor response to electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC)

<table>
<thead>
<tr>
<th>Patient</th>
<th>ePIPAC 1</th>
<th></th>
<th>ePIPAC 2</th>
<th></th>
<th>ePIPAC 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive cytology</td>
<td>Mean PRGS</td>
<td>Positive cytology</td>
<td>Mean PRGS</td>
<td>Positive cytology</td>
<td>Mean PRGS</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>3.50</td>
<td>Yes</td>
<td>2.66</td>
<td>Yes</td>
<td>2.66</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>1.50</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>2.50</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>2.00</td>
<td>No</td>
<td>1.50</td>
<td>Yes</td>
<td>2.50</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>1.00</td>
<td>No</td>
<td>1.00</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>1.50</td>
<td>Yes</td>
<td>2.50</td>
<td>Yes</td>
<td>2.00</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>2.00</td>
<td>Yes</td>
<td>1.75</td>
<td>Yes</td>
<td>1.00</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>2.00</td>
<td>No</td>
<td>1.00</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>2.00</td>
<td>No</td>
<td>1.00</td>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>2.25</td>
<td>No</td>
<td>2.25</td>
<td>Yes</td>
<td>2.25</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>1.33</td>
<td>No</td>
<td>1.00</td>
<td>Yes</td>
<td>2.66</td>
</tr>
</tbody>
</table>

PRGS: Peritoneal Regression Grading Score

Table 4. Adverse reactions to electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC) according to Common Terminology Criteria for Adverse Events (v. 4.0)

<table>
<thead>
<tr>
<th>CTCAE grade</th>
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<tbody>
<tr>
<td>ePIPAC</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>
4.0 Discussion

This is the first prospective study on ePIPAC. It was designed to investigate if the histological response to ePIPAC with one minute of electrostatic precipitation was similar or better than the response to standard PIPAC directed treatment with 30 minutes of simple diffusion. The histological tumor response was assessed through repeated peritoneal biopsies using the PRGS [14]. The main finding of this study was that ePIPAC with one minute of electrostatic precipitation did not provide a satisfactory histological response, when compared to data from the prospective PIPAC-OPC1 study [4], where 11 percent had histological disease progression. Secondarily, this study showed that one minute ePIPAC was repeatable and easily performed with a low adverse events profile and no mortality, which is in agreement with a recently published feasibility and efficacy study, where 48 patients had 135 ePIPAC procedures due to PM from different primary tumors [15].

The amendment to the PIPAC-OPC2 study was initiated and approved based on the assumption that one minute ePIPAC was feasible and able to induce an equivalent or better histological response than standard PIPAC with 30 minutes diffusion time, while ensuring a shorter period of general anesthesia for the patients. Even though the visual field was cleared and the aerosol had disappeared within a few seconds in all patients, four in ten patients had disease progression according to the PRGS at the third ePIPAC procedure. Based on these findings, and according to the predefined criteria, the study was terminated after the first ten patients, and the remaining patients in the PIPAC-OPC2 study will receive standard PIPAC with a diffusion time of 30 minutes.

The strategy of performing ePIPAC with only one minute of diffusion and electrostatic precipitation in patients with PM might have been too premature. However, histological treatment response was seen in four of ten patients, thus implying that the short treatment time helped some patients. To date at least four animal models have been developed to test repartition, penetration and droplet size during PIPAC [7, 16-18], and despite the limitations of animal models, it would have been of interest to test the results of one minute diffusion and electrostatic precipitation in such models.

This study is limited by a low number of patients since it was stopped at the second interim analysis. However, the statistical preparation of the study showed that progression in three or more out of ten patients would be statistical significant with a p-value of 0.02. There was no optimal evaluation of treatment response in the patients with PM. The visual evaluation of treatment response during PIPAC could have been documented by the Peritoneal Cancer Index (PCI) [19, 20].
We chose not to, since the laparoscopy was performed through only two trocars and since visual mapping and response assessment was hampered by severe adhesions and peritoneal fibrosis [4, 21]. The PCI was calculated at the index PIPAC procedure to describe the study population. Radiological evaluation according to RECIST was not possible due to the low-volume PM elements that were deemed non-measurable. One study is currently investigating if diffusion-weighted gadolinium enhanced magnetic resonance imaging is useful in the response evaluation of PIPAC directed treatment [22]. As such, the study was limited by the unidimensional response evaluation based on the histological PRGS. The clinical and prognostic impact of the PRGS evaluation has not been validated so far. Still, the intra- and interobserver variability of the PRGS is good [23] and at the moment PRGS seems to be the only validated tool for histological tumor response evaluation. The study populations of both the present study and the PIPAC-OPC1 “control group” were heterogeneous, since patients had different primary tumors and had received different lines and types of chemotherapy before inclusion. Further, a substantial number of patients received bidirectional treatment which makes it impossible to separate treatment response to ePIPAC and systemic chemotherapy. Patients were treated with oxaliplatin or low-dose cisplatin and doxorubicin despite the recently published dose-escalation study on cisplatin and doxorubicin [24], but since the entire procedure and setup (apart from the one minute electrostatic precipitation) should resemble the setup in the PIPAC-OPC1 study, the same dose of chemotherapy was used.

These limitations show that data must be analyzed with caution, and that the external validity of these data is compromised. The ePIPAC modification to the standard PIPAC directed treatment will probably still show promising and improved results in terms of oncological and patient related outcomes in future studies, but in this study one minute ePIPAC lacked sufficient histological response. Future studies should focus on the optimal treatment time after turning on the electrostatic precipitation, ideally starting at 30 minutes and then reducing the time frame stepwise. Based on the current evidence and heterogeneity of ways to determine treatment response, more phase two studies are needed before embarking on large randomized controlled trials.
5.0 Conclusions

One minute ePIPAC was easily performed, feasible and safe, but the histological tumor response assessed in repeated peritoneal biopsies was inferior compared to standard PIPAC directed treatment with 30 minutes passive diffusion time.

**Declarations of interest:** none

**References**

**Figure 1.** Electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC). The nebulizer is inserted through the 12 mm trocar and the laparoscope through the five mm trocar. A brush electrode (Ionwand, Alesi Surgical Ltd., UK) is inserted within the visual field. The brush electrode emits electrons that charge the aerosolized chemotherapy negatively, thereby creating a current gradient towards the return electrode.

**Figure 2.** Patient flow during electrostatic precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC) directed treatment.

Below figure: PM: Peritoneal metastasis, PRGS: Peritoneal Regression Grading Score
1st ePIPAC, n=33

- Non-access 3
- Clinical progression 2
- Liver metastases 1
- Patient demand 3
- Death 2
- ePIPAC abandoned 4

2nd ePIPAC, n=18

- Clinical progression 4
- Progression of PM 2

3rd PIPAC, n=12

- Protocol violation 2

PRGS Response Evaluation, n=10