Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): A localized Drug Delivery Approach to Treat Peritoneal Carcinomatosis of Different Origins

By

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A thesis submitted to the School of Pharmacy in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited full and accurate referencing.

3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.

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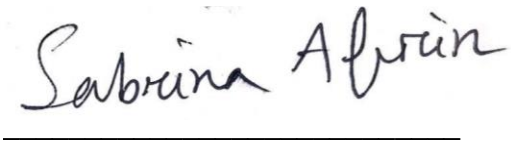

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Approval

The thesis titled "Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): A localized Drug Delivery Approach to Treat Peritoneal Carcinomatosis of Different Origins" submitted by Sabrina Afrin (18146080), of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics statement

Any animal or human trials were not involved in this project.

Dedication

I am dedicating this work to my respected project supervisor, Tanisha Momtaz, Lecturer, School of Pharmacy, Brac University, who has inspired me incredibly from the very beginning of this project.

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Abstract

Pressurized Intraperitoneal Aerosol Chemotherapy or PIPAC has recently gained focus of researchers worldwide in the field of oncology for treating the notorious cancer peritoneal carcinomatosis. The aim of this review was to present a scientific overview of PIPAC for treating peritoneal carcinomatosis of different origins. The methodology of the research was based on reviewing the available scientific literature from reliable online resources. High pressure and aerosol dosage form are utilized in PIPAC to deliver chemotherapy intraperitoneally. Oxaliplatin and a combination of cisplatin followed by doxorubicin are the most frequently administered drugs in PIPAC. PIPAC exerts a high local activity with lower systemic effects. PIPAC has shown substantial tumor regression and efficacy. Some major and frequent minor adverse effects have been identified. Larger clinical trials are needed to clearly define the indications of PIPAC, assess its long-term toxicity, and expand its clinical use in the treatment of peritoneal carcinomatosis.

Keywords: Pressurized Intraperitoneal Aerosol Chemotherapy, PIPAC, peritoneal carcinomatosis, cancer, oncology, drug delivery, intraperitoneal chemotherapy, anti-cancer agents.

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List of Acronyms

5-FU: Fluorouracil

APA: American Psychological Association

CAWS: Closed aerosol waste system

CFD: Computational fluid dynamics

CRS: Cytoreductive surgery

DNA: Deoxyribonucleic acid

DSRCT: Desmoplastic small round cell tumor

ECG: Electrocardiograph

EORTC: European Organisation For Research And Treatment Of Cancer

ePIPAC: Electrostatic precipitation pressurized intraperitoneal aerosol chemotherapy

ePIPAC-OX: Electrostatic pressurized intraperitoneal aerosol chemotherapy with oxaliplatin

Nab-pac: Albumin bound nanoparticle paclitaxel

FDG PET-CT: Fluorodeoxyglucose Positron Emission Tomography-CT

GI: Gastrointestinal

HEPA filter: High-efficiency particulate air filter

HIPEC: Hyperthermic intraperitoneal chemotherapy

IDEAL: Idea, Development, Exploration, Assessment, Long-term study

IP: Intraperitoneal

MRI: Magnetic resonance imaging

NA: Not applicable

NAB-PTX: Nanoparticle albumin-based paclitaxel

PC: Peritoneal carcinomatosis

PCI: Peritoneal carcinomatosis index

PIPAC: Pressurized Intraperitoneal Aerosolized Chemotherapy

PPSC: Primary peritoneal serous carcinoma

PRGS: Peritoneal Regression Grading Score

PSI: Pounds per square inch

QLQ30: Quality of Life Questionnaire

QOL: Quality of life

TIVA: Total intravenous anaesthesia

USFDA: U.S. Food and Drug Administration

Chapter 1: Introduction

1.1 Peritoneal carcinomatosis

Peritoneal carcinomatosis is a lethal cancer type that affects the peritoneum. It has a remarkably poor prognosis, which indicates a low possibility of recovery from the disease. Hence peritoneal carcinomatosis is a challenging disease in the vast field of oncology (Lambert, 2015). It is known that the parietal peritoneum and visceral peritoneum constitute the peritoneum. The mesothelial membrane that lines the abdominal cavity's inner surface is known as the parietal peritoneum. The visceral peritoneum is the extension of the peritoneum that covers different organs and the majority of the intestine and the cavity between the visceral and parietal membranes of the peritoneum is denoted as the peritoneal cavity. Intraperitoneal organs are organs that are covered with the peritoneum (Raptopoulos & Gourtsoyiannis, 2001). Peritoneal carcinomatosis, shortly named PC, is a condition in which metastasis and deposition of tumors occur on the peritoneal surface. It is considered to be a late-stage complication of numerous gastrointestinal cancers such as gastric, colorectal, appendiceal cancer, etc. In most cases, only palliative care options are available to patients with PC, which are intended to alleviate the symptoms (McMullen et al., 2017). At an early stage, peritoneal carcinomatosis can be completely asymptomatic. Symptoms including abdominal pain, nausea, loss of weight, bloating, diarrhea, etc. may occur following the advancement of the condition (Levy et al., 2009). It is quite difficult to diagnose small volume PC at an early stage. In most cases, patients are diagnosed with PC during a laparotomy performed due to a known primary gastrointestinal cancer. Large ascites, partial bowel obstruction, or inanition may be observed in patients with a high tumor burden (Royal & Pingpank, 2008). Different scoring methods are used for intraoperative staging of PC, these include- the Sugarbaker peritoneal carcinomatosis index (PCI), Gilly classification, P score, and Verwaal N score method

(Brcher et al., 2012). Imaging tools applied in the diagnosis of PC are computerized tomography, magnetic resonance imaging (MRI), ultrasound, and 18F-Fluorodeoxyglucose Positron Emission Tomography-CT or FDG PET-CT. However, all of these imaging tools have significant drawbacks in terms of accurate diagnosis of PC. Therefore, the major diagnostic procedures in PC are peritoneal cytological examination, laparotomy, and laparoscopy (Montori et al., 2014). Early detection of this cancer and identification of people with a higher risk of PC can facilitate treatment. In systematically selected patients, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown promising survival results (Chia et al., 2016). In spite of the advancements in the management of peritoneal carcinomatosis, there are low survival outcomes and elevated morbidity rates. There are debilitating complications of this disease, such as - anorexia, fatigue, enteric fistulae, dysmotility, bowel obstruction, ascites, abdominal pain, ureteral or biliary obstruction, cachexia, etc. (Lambert & Hendrix, 2018). A study of PC of colorectal origin showed that cytoreduction with HIPEC resulted in median survival of 21 months (Verwaal et al., 2004). PC arising from gastric origin shows median survival of approximately one to three months. Peritoneal carcinomatosis causes death in 53–60% of patients with gastric cancer (Montori et al., 2014).

1.2 Inception of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

In November 2011, a new drug delivery method named pressurized intraperitoneal aerosol chemotherapy (PIPAC) was first reported for the chemotherapeutic treatment of peritoneal cancer. The tolerance, practicality, and outcomes of this drug delivery approach have gathered the focus of the scientific community globally. One of the major problems in peritoneal carcinomatosis is the low response to systemic chemotherapy. PIPAC has arisen as a new approach to achieving

higher tissue concentration and decreasing systemic toxicity in peritoneal carcinomatosis (Alyami et al., 2019a). In intraperitoneal (IP) chemotherapy approaches, chemotherapeutic drugs are directly administered into the abdominal cavity to obtain higher effectiveness. In the case of pressurized intraperitoneal aerosol chemotherapy (PIPAC), chemotherapeutic drugs are delivered in an aerosol dosage form in a low dose by applying high intraperitoneal pressure using a laparoscopic system. Higher penetration has been accomplished along with decreased systemic toxicity in studies using PIPAC (Oh et al., 2021a; C. B. Tempfer, 2015). The existing technique in this field before the invention of PIPAC was hyperthermic intraperitoneal chemotherapy (HIPEC). Although HIPEC has its own advantages, it has the limitation of inadequate tumor penetration depth of 1 to 5 mm. Due to the cylindrical anatomy of the abdominal cavity, the distribution of the chemotherapeutic drugs is not uniform with HIPEC. Moreover, renal and hepatic toxicity is a concern with this technique (Oh et al., 2021a; C. B. Tempfer et al., 2014). Hence new technologies in intraperitoneal chemotherapy delivery such as PIPAC may pave the way for alternative treatment options in specific clinical conditions for patients with peritoneal carcinomatosis.

The most prevailing implementation of PIPAC reported in 2021 is for gastric, colorectal, and ovarian cancers. There have also been occasional reports of the use of PIPAC in unresectable peritoneal cancers arising from primary tumors, for example, pseudomyxoma peritonei, mesothelioma, pancreatic and hepatobiliary tumors. The chemotherapy drugs incorporated most frequently using the PIPAC delivery system in the case of humans are cisplatin, doxorubicin, and oxaliplatin. Due to the use of aerosolized cytotoxic drugs in the application of PIPAC, there is a preliminary alarming issue regarding the exposure of these toxic substances to operating room personnel. But it has been observed that following stringent safety precautions in the application

of PIPAC minimizes this risk for operating room personnel significantly (R. J. Lurvink et al., 2021a).

Despite the promising results achieved so far with PIPAC technology, there is a necessity for further investigation of this drug delivery method in order to explore its merits and demerits in the treatment of peritoneal carcinomatosis and to adopt PIPAC more extensively in clinical practice globally. Therefore, further clinical trials and relevant studies should be conducted soon in order to validate its application to a greater extent and to address its limitations.

1.3 Rationale:

The rationale of this study is to investigate a better treatment option compared to conventional approaches for patients with peritoneal carcinomatosis. As peritoneal carcinomatosis patients are have poor prognosis, novel technology needs to be explored for providing better therapeutic outcomes.

1.4 Significance:

As PIPAC in the treatment of peritoneal carcinomatosis of different origins has been reviewed in this study, it provides up-to-date information and discussion on the clinical application of PIPAC for this particular disease. Such findings contribute to assess the benefits, demerits, feasibility of this new technology in oncology. Novel technologies like PIPAC may improve the quality of life of selective peritoneal carcinomatosis patients. Moreover, the challenges and their solutions investigated in this study for implementing PIPAC can facilitate further development and adaptation of this therapy globally.

1.5 Aims

The aim of this research is to provide a scientific overview of pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in the treatment of peritoneal carcinomatosis. Since peritoneal carcinomatosis is a fatal condition that has limited treatment options and a poor prognosis, experimentation with novel technologies like PIPAC can widen the treatment choices and improve the therapeutic outcomes for peritoneal carcinomatosis patients.

1.6 Objectives

The objectives of this research include, firstly, comprehending the pathophysiology of peritoneal carcinomatosis and chemotherapeutic agents used in its treatment. Secondly, the technical aspects of intraperitoneal drug delivery administration in PIPAC will be discussed. Thirdly, the positive and negative outcomes observed in patients undergoing PIPAC in studies will be summarized. Fourthly, a comparison of PIPAC with existing treatment strategies will be provided. Finally, future aspects including challenges with the application of PIPAC and possible ways to overcome those challenges will be addressed.

Chapter 2: Methodology

Reliable online sources of scientific literature such as PubMed of the National Library of Medicine and Google Scholar were used to search for scholarly articles on PIPAC and the disease of interest-peritoneal carcinomatosis. Searching the terms ((Pressurized Intraperitoneal Aerosolized Chemotherapy) OR (PIPAC)) AND (Peritoneal Carcinomatosis) using the advanced search builder in Pubmed at https://pubmed.ncbi.nlm.nih.gov/ without applying any filter showed 194 results from 2000-2022. After filtering 'clinical trial' and 'randomized controlled trial' as article types, 10 original research articles were found. 35 articles appeared when 'review' and 'systematic review' were filtered regarding the topic. Moreover, a total of 25 studies were found regarding PIPAC and peritoneal carcinomatosis on the online database of ClinicalTrials.gov, which is a database of clinical trials performed privately and publicly worldwide. Articles published by a wide variety of scientific journals were interpreted in order to collect relevant up-to-date information. This available literature aided to answer the research questions regarding peritoneal carcinomatosis and PIPAC. The synthesized information of this review was then systematically compiled. All information taken from different sources was credited and cited appropriately according to APA 7th referencing style using the Mendeley Desktop version 1.19.8 software.

Chapter 3: Peritoneal carcinomatosis

3.1 Pathophysiology of Peritoneal carcinomatosis

The pathophysiology of peritoneal carcinomatosis can be defined by three main molecular pathways. These are- 1) dispersal from the primary tumor, 2) primary tumor in the peritoneum and 3) polyclonal tumor origin. These three mechanisms can occur individually or also can occur together within a single occurrence.

1) Dispersal from primary tumor:

In this pathway, dispersal of tumor begins with the original tumor and it comprises several steps. At the beginning, single or multiple tumor cells need to separate from the original tumor in order to reach the peritoneal cavity. This separation can take place by a few mechanisms. A common mechanism in gastrointestinal cancer is tumor cell exfoliation which infiltrates the serosa. There are adhesion molecules present on the surface of tumor cells such as E-cadherin which is down-regulated in this mechanism (Kusamura et al., 2010). During surgical operation the transection of blood vessels and lymphatics or rupture of primary tumor iatrogenically can also cause access of the original tumor cell inside the peritoneal cavity (Kostić et al., 2006). There are three types of forces which aid dissemination of tumor cells in different parts of the abdomen. These are- peristalsis of GI tract, gravity, and negative pressure due to diaphragm. Metastasis can occur in trans-mesothelial and trans-lymphatic pathways. Liberated tumorous cells attach to mesothelium with the help of adhesion molecules (Jayne, 2003). The transmembrane receptors named integrins aid the adherence of cancer cells to the sub-mesothelial connective tissue (Kawamura et al., 2001). Then the tumor cells invade the sub-peritoneal layer as the peritoneal blood barrier is crossed. Eventually cancer cells stimulate its proliferation via autocrine/paracrine loops. Aside from this trans-mesothelial pathway, dispersal of tumor may also follow trans-lymphatic route. In the trans-

lymphatic route free peritoneal tumor cells reach sub-peritoneal lymph spaces via the lymphatic stoma (Kusamura et al., 2010).

2) Primary tumor in peritoneum:

Infrequent abrasions derived from mesothelial or sub-mesothelial peritoneal layers are called primary peritoneal tumors. This can be further differentiated into- multicystic mesothelioma, desmoplastic small round cell tumor (DSRCT), malignant mesothelioma, leiomyomatosis peritonealis disseminata, primary peritoneal serous carcinoma (PPSC) etc. Tumors that are primarily manifested in peritoneum are named as primary peritoneal tumors (Levy et al., 2008). This has often been associated with asbestos exposure. In asbestos carcinogenesis three processes have been suggested. The first one relates to the formation of free radicals by asbestos which affect DNA and in turn cause cancer. Secondly, excess production of free-radicals, cytokines, growth factors due to asbestos induced chronic inflammation may cause primary peritoneal tumors. Thirdly the asbestos fibers can exaggerate the carcinogenic action of other chemical carcinogens by working as vectors (Mirarabshahii et al., 2012).

3) Polyclonal tumor origin:

When two or more non-identical progenitor clones are responsible for the formation of a tumor, the origin of the tumor is called polyclonal (Parsons, 2008). In the traditional theory of peritoneal carcinomatosis and carcinogenesis, there are some controversies present. It states that genetic changes lead to hyperproliferation, lower apoptosis, and higher dedifferentiation. But according to cancer stem cell theory, a minimal quantity of proliferative cells can self-renew and differentiate into several lineages. Which is the opposite of the traditional theory. The polyclonal origin of the

tumor can be explained by mutation of stem cells in the embryonic stage which stays dormant and is later stimulated by environmental influences. This model can address the pathophysiology of the following tumors which show peritoneal spread- peritoneal extra ovarian papillary serous carcinoma and ovarian tumors having a low malignant capacity (Bejan & Scripcariu, n.d.; Pereira et al., 2015).

3.2 Association of Peritoneal carcinomatosis with other cancers

Peritoneal carcinomatosis is often associated with disease progression of several other types of cancers. Association of peritoneal carcinomatosis with other cancers is discussed below:

Colorectal cancer: In colorectal cancer patients, the occurrence of peritoneal carcinomatosis is very common. A study aimed to assess the presence of PC in colorectal cancer patients was conducted using an extensive database. In the database, 3019 patients with colorectal cancer were selected. Here, 349 patients, or 13% were also found with PC (Jayne et al., 2002). Another study reported that patients who have isolated colorectal cancer, 15 to 20% of such patients developed PC. Moreover, 20 to 30% patients develop PC who have colorectal cancer along with other localization for example liver cancer (Piso & Arnold, 2011).

Gastric cancer: In gastric cancer patients, a significant reason for mortality and morbidity is considered to be peritoneal carcinomatosis. In a 1995-2011 study of gastric cancer patients in the Eindhoven Cancer Registry, gastric cancer was diagnosed in 5220 patients. 2029 of these patients were in a metastatic state. Among these patients, 706 or 14% developed PCs. Median survival in gastric cancer patients was 14 months whereas gastric cancer along with PC showed survival of only four months. Thus, development of PC in gastric cancer patients decreased median survival remarkably (Thomassen et al., 2014).

Ovarian cancer: In dissemination of ovarian cancer one of the most frequent paths is peritoneal seeding. Since most ovarian cancers are epithelial, some cancer cells may gain access to peritoneal circulation. Peritoneal fluid carries ovarian tumor cells via pelvis and abdomen and consequently spreads further (Pannu et al., 2003).

3.3 Chemotherapeutic agents used in peritoneal carcinomatosis:

Numerous chemotherapeutic agents have been studied in clinical trials for their potential as intraperitoneal chemotherapy to treat peritoneal carcinomatosis. These include- doxorubicin, mitomycin C, melphalan, cisplatin, gemcitabine, oxaliplatin, carboplatin, mitoxantrone, irinotecan, etoposide, docetaxel, paclitaxel, 5-fluorouracil, floxuridine etc. A brief description of some of these important agents are presented here.

1) Cyclophosphamide: Cyclophosphamide was initially the only chemotherapeutic drug which had USFDA (U.S. Food and Drug Administration) approval for intraperitoneal use. But the usage of cyclophosphamide intraperitoneally is problematic since the drug requires it to be activated by liver microsomal enzymes (Sugarbaker et al., 2005).

2) Doxorubicin: Doxorubicin was among the first chemotherapy drugs studied in humans for intraperitoneal administration. Its compatibility to be given in combination with different chemotherapy drugs makes it a useful anticancer treatment in treating PC. There is also a lower chance of systemic adverse effects since doxorubicin is partly biotransformed via single hepatic pass (Jacquet et al., 1996).

3) Melphalan: The anticancer agent melphalan shows significantly better response in peritoneal tumors when administered in the intraperitoneal route rather than systemically. The tolerated dose of melphalan is increased if it is given intraperitoneally (Howell et al., 1984). In another study of 34 patients, melphalan was found to be a suitable chemotherapeutic drug for HIPEC in terms of safety and efficacy (Bijelic et al., 2012).

4) Cisplatin: Cisplatin is well-studied for both hyperthermic and non-hyperthermic intraperitoneal usage. It is the most frequent choice of drug for HIPEC. Application of hyperthermia in intraperitoneal administration of cisplatin showed synergic action, thus improving cytotoxicity and effectiveness of cisplatin. Cisplatin offers a desirable peritoneal plasma gradient (yun Wang et al., 2021). This alkylating drug induces apoptosis via the generation of DNA adducts and thereby exerts its anticancer effects (Lemoine et al., 2017).

5) Gemcitabine: The preventive benefits of the intra-operative application of gemcitabine in PC was experimented in studies. These studies show that intra-operative usage of gemcitabine in the abdominal cavity has the potential in the prevention of peritoneal cancer (Ridwelski et al., 2002).

6) Mitomycin C: Mitomycin C is another feasible drug for peritoneal carcinomatosis due to its advantageous area under curve ratio of intraperitoneal concentration time and plasma concentration. It is commonly given with hyperthermia. Compared to plasma level via systemic administration of Mitomycin C, studies have shown a 107-fold elevation when the route of administration is intraperitoneal (Shen et al., 2004).

Chapter 4: Intraperitoneal drug delivery approach of PIPAC

4.1 Challenges in intraperitoneal chemotherapy delivery

A number of factors make intraperitoneal (IP) chemotherapy delivery challenging. These challenges include- inadequate penetration of drugs, rapid clearance of small molecule drugs from the peritoneal cavity, inadequate target specificity, etc (Bajaj & Yeo, 2010).

Rapid clearance from the peritoneal cavity:

In order for a drug to be active in the peritoneal cavity for sufficient time, the residence time of the drug in the peritoneal cavity needs to be long enough and avoid rapid clearance. However, drugs having molecular weights of less than 20kDa exhibit low residence time, which can result in requiring repeated and continual dosing. This can in turn result in catheter-related complications for example bowel complications, catheter blockage, higher incidence of infections. Moreover, some small molecule drugs are able to access systemic circulation via the peritoneal capillaries, which is undesirable (Poveda et al., 2007).

Inadequate drug penetration:

Vascular hyperpermeability is the process of excess fluid and protein drainage from blood vessels into the interstitial space. Due to this excessive interstitial fluid pressure exhibited by hyperpermeability of blood vessels and the shortage of lymphatics, the penetration of drugs in the peritoneum is inadequate (Jain, 2001; Oakley & Tharakan, 2014).

Peritoneal toxicity:

If the anticancer drug does not have high specificity toward the target tumors in the peritoneal cavity, then there is a higher chance of developing peritoneal toxicity. This is because the chemotherapeutic agents may adversely affect the normal tissue of the peritoneum as well in a dose-dependent manner. Local high concentration of drugs in the peritoneum due to intraperitoneal

administration may create peritoneal toxicity. Thus, achieving high target specificity is another challenge in IP chemotherapy (Bajaj & Yeo, 2010).

Other challenges in IP chemotherapy:

Drug particles often enter the lymphatic system from the peritoneal cavity, which can cause the destruction of these drug particles by lymphocytes. Another problem in the case of large drug molecules is peritoneal adhesion (Kohane et al., 2006). Finally, a general challenge for all chemotherapeutic agents is multidrug resistance. Multidrug resistance is one of the major reasons that can hinder the positive outcomes of chemotherapy ("Cancer Multidrug Resistance," 2000).

Solutions to overcome challenges in IP drug delivery:

The inadequate residence time of drugs in the peritoneal cavity can be improved by formulating microparticles. Experiments revealed that microparticles ranging between 4 to 47 μm showed better results in IP drug delivery in terms of residence time (Tsai et al., 2007). The usage of viscous polymer solutions or hydrogels for the carrier of drugs can also improve the residence time (Mohamed et al., 2003). In order to avoid lymphocytic destruction, liposomal drug formulations can be used since liposomes are not affected by lymphocytes (Hlrano & Anthony Hunt, 1985). Multidrug resistance may also be overcome by utilizing colloidal drug carriers such as nanoparticles or liposomes (Bajaj & Yeo, 2010).

4.2 Surgical procedure for administering PIPAC

A substantial level of standardization has been implemented at PIPAC treatment centers for different technical aspects of administering PIPAC including the surgical procedure and safety measures (Alyami et al., 2019a). A laparoscopic method is used for PIPAC. The patient is given general anesthesia in the operating room before the procedure of PIPAC is started. Like

laparoscopic procedures, incisions are made during PIPAC. The general anesthesia is given so that the patient does not feel pain or discomfort during the whole procedure. The antibiotics-metronidazole and cefuroxime are suggested as a prophylactic measure (*Peritoneal Carcinomatosis from Non-Gynecologic Malignancies: Results of the EVOCAPE 1 Multicentric Prospective Study - PubMed*, n.d.). A visual presentation of the procedure of PIPAC is shown in figure 1. A 5mm optical trocar and a 10mm to 12mm nebuliser are utilized for accessing the abdomen region. Most frequently, a lateral trocar (11mm) and a 12mm trocar for the median infra-umbilical line are used. Incidental mobilization or evasion of the chemotherapeutic agent is prevented with the help of Hasson trocars which have single or double balloons (Nowacki et al., 2018). In further therapies, the same incisions are utilized. Maintaining a standard pressure of 12 mm Hg, carbon dioxide is insufflated into the abdomen. Since ascites are a common complication in peritoneal carcinomatosis, ascites is measured. Peritoneal flushing is performed if there are no signs of ascites. A fluid sample is collected for cytological examination. The peritoneal cancer index (PCI) is assessed by examining the abdominal cavity region. Biopsy forceps are used for collecting at least three biopsies. A 30-degree optical instrument enables proper visualization of the procedure through video (Sugarbaker & Ryan, 2012). There are four abdominal quadrants and it is suggested that biopsies are carried out for all four quadrants. This is because when biopsies are taken from right upper, right lower, left upper and left lower quadrants of the abdomen it will help to detect presence of cancer cells more accurately upon pathological examination. Moreover, the histology findings can be improved with a 2×2 peritonectomy (Solass et al., 2016). Using a high-pressure injector and nebulizer (standardized for PIPAC), intraperitoneal chemotherapy is injected and administered in an aerosol form. The injector is set with a flow rate of 0·5–0·7 mL/s and maximal upstream pressure of 290 psi. The nebulizer usually used is Capnopen. The

chemotherapeutic drug usually applied is either only oxaliplatin or cisplatin followed by doxorubicin. The capnoperitoneum is sustained for a period of 30 minutes. Then the remaining aerosol is removed in a closed aerosol waste method. Two microparticle filters are present in the wall outlet to aid this aerosol removal (Cazauran et al., 2018; Graversen et al., 2016). Accidental leakage can cause a risk of exposure to chemotherapy to the operating room personnel. Thus measures must be taken to prevent carbon dioxide leakage using pneumoperitoneum restraint (Foster et al., 2019). An operation room with laminar airflow is recommended. Moreover, an aseptic plastic cover linked with a HEPA (high-efficiency particulate air) filter can be used to cover the patient. The medical team should be outside of the room. Through a window, the anesthesiologist constantly observes the patient (Hübner et al., 2017). It is important that syringes, trocars, chemotherapy materials, serum and any other disposables are discarded at the end of the according to appropriate disposal protocols (Akaishi et al., 2021a).

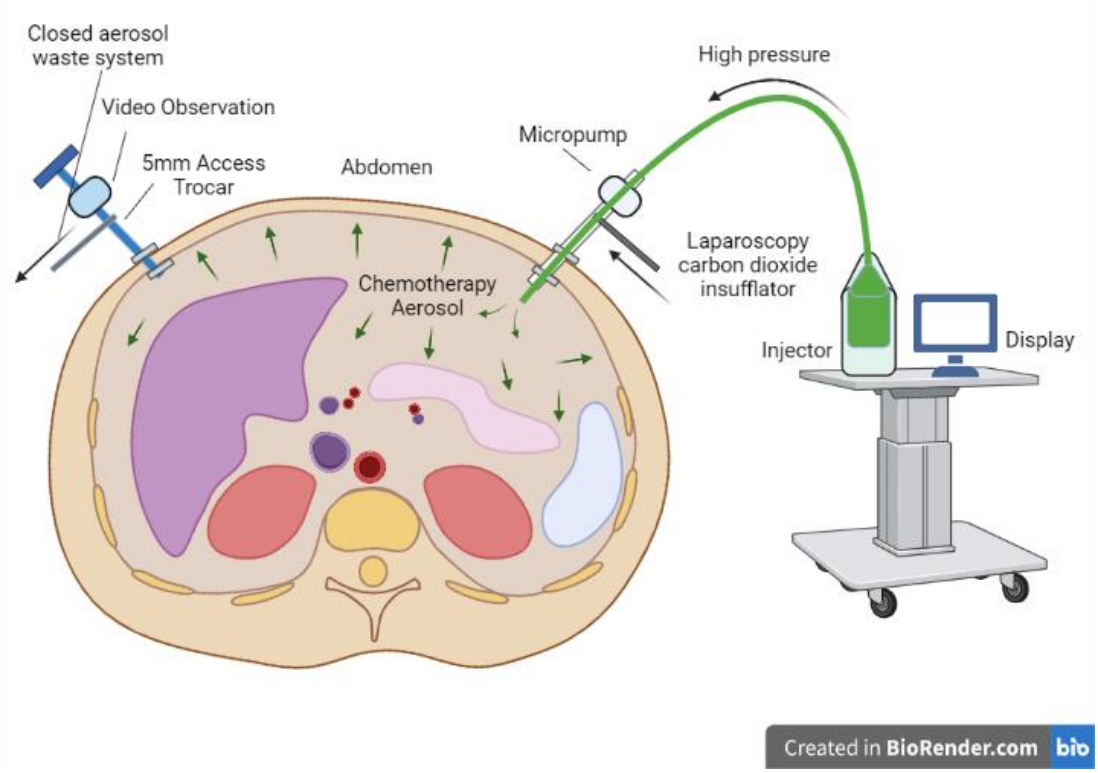

Figure 1: Visualization of chemotherapy delivery in PIPAC (Alyami et al., 2019b).

4.3 Anesthesia considerations for the administration of PIPAC

The anesthetic considerations that should be undertaken for the administration of PIPAC are summarized in table 1.

Table 1: Anesthesia considerations for the administration of PIPAC (Shree et al., 2020).

Sl.	Category	Considerations
1.	Location of procedure	• Operation theater should have appropriate ventilation system. • Induction room should be sealed to prevent dissemination of cytotoxic fumes. It should allow remote monitoring of patient, emergency access of staff • A monitor should present vital signs of patient both inside and outside the operation theater.
2.	Pre-operative preparations	• Detailed patient history must be taken to confirm whether patient matches the inclusion or exclusion criteria of PIPAC. • Routine pre-anesthesia examination should be performed. • Closed Aerosol Waste System (CAWS) must be used for evacuating remaining chemotherapeutic agent from the abdomen. • Total intravenous anaesthesia (TIVA) should be applied for induction and maintenance. • Patient should be counseled about the procedure.
3.	Monitoring & Equipment	• The following monitoring should be done- 1. Electrocardiograph (ECG) 2. Pulse oximetry 3. Capnography 4. Blood pressure 5. Depth of anaesthesia monitor • Anaesthesia machine with ventilator • Extension lines for drug infusion
4.	Required drug types	• Premedication or antiemetics • Anesthetic agent • Paralytics • Analgesics

4.4 Mechanism of drug delivery in PIPAC

Medicinal aerosols have been extensively studied in the field of pulmonary drug delivery. However, the mechanism of drug delivery using aerosols in the case of intraperitoneal drug delivery has not been as vastly explored.

It is known from the theory of a perfect gas that gas molecules come into collision with each other and with surrounding walls as they move in random directions. Pressure is created per unit area due to such collisions. As a result, a uniform distribution of the gas occurs in the available volume. The final dosage form in PIPAC is an aerosol, where particles or liquid droplets are suspended in a gas. Although an aerosol shows less uniform spatial distribution compared to a gas, aerosol shows a higher uniformity compared to a liquid (Nadiradze et al., 2019). A number of variables influence the action of medicinal aerosols. These variables include- size distribution, median aerodynamic diameter, partitioning, coagulation, activation, terminal velocity, dynamics, etc. The deposition of aerosols is affected primarily by the laws of gravitational sedimentation and inertial impaction. Gravitational sedimentation is the main mechanism of deposition that occurs in the peritoneal cavity (Hinds & Zhu, 2022). In PIPAC, pressurized carbon dioxide is introduced in the peritoneum, which is a state called capnoperitoneum. Due to this capnoperitoneum, it is easier for microdroplets of the active drug to reach any exposed surface in the peritoneum (Solaß et al., 2012). A visual comparison of the mechanism of PIPAC and liquid non-pressurized intraperitoneal chemotherapy is presented in figure 2. In the figure, # represents drug penetration and h represents the height of liquid chemotherapy. In the case of liquid chemotherapy, gravitational force (F1) exerted on tumor nodes is dependent on ‘h’. Also, the contact of tumor nodes with liquid chemotherapy depends on the volume of the liquid filled. In the case of PIPAC, a combination of monodirectional gravitational force (F1) and multidirectional hydrostatic pressure (F2) is exerted

due to the application of high pressure. The aerosol is able to reach all exposed surfaces. Liquid chemotherapy tends to move towards normal tissue instead of tumor node since there is less resistance in normal tissue. Whereas aerosol of PIPAC enters both the tumor node and normal tissue (Nadiradze et al., 2019).

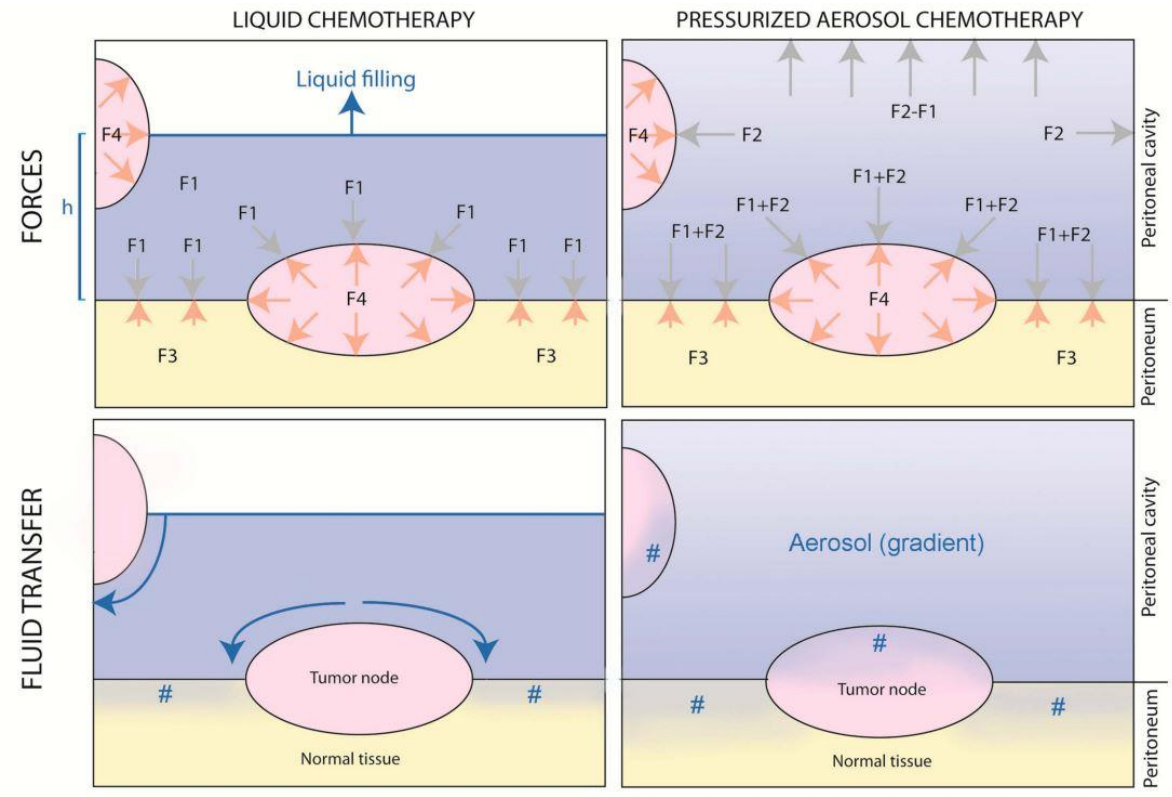

Figure 2: Visual comparison of the mechanism of PIPAC and liquid non-pressurized intraperitoneal chemotherapy (Nadiradze et al., 2020a).

The entry of large molecules and drugs into the systemic circulation is prevented by the peritoneal–plasma barrier. Therefore, elevated drug concentrations can be achieved locally in the peritoneal cavity while avoiding systemic adverse effects (De Bree et al., 2017).

4.5 Drugs selection

Since PIPAC is still in its early stages of clinical trials, only a few chemotherapeutic agents have been utilized in this technology so far. A majority of the ongoing or completed studies on PIPAC have selected oxaliplatin alone or cisplatin followed by doxorubicin as chemotherapeutic agents. Some recent studies of PIPAC are experimenting with the drug paclitaxel. It is expected that the options for drug selection in PIPAC will widen in the future when more clinical trials are completed with other chemotherapy drugs. (Alyami et al., 2019a; Ceelen et al., 2022a).

The percentage of different drugs involved in clinical trials of PIPAC that are recorded in ClinicalTrials.gov is presented in figure 3.

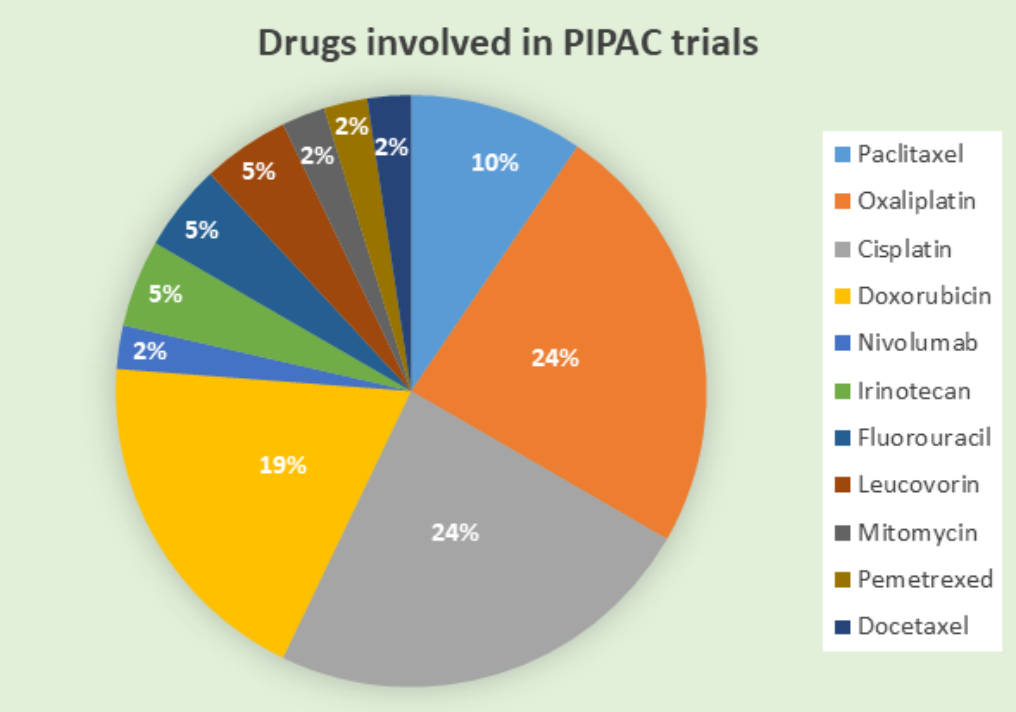

Figure 3: Percentage of different drugs involved in clinical trials of PIPAC (ClinicalTrials.gov, n.d.).

4.6 Drug formulation characteristics

In PIPAC drug delivery, a formulation in solution form is aerosolized using an appropriate nebulizing device. At present, PIPAC incorporates solution formulations having a high viscosity. Such formulations include- lipophilic, polymer, protein, nucleic acid, carbohydrate solutions, etc (M. A. Reymond et al., 2000). This cytotoxic solution contains approximately 10 to 20% of a usual systemic chemotherapy dose. The drug formulation for PIPAC does not require any propellant gas, unlike the formulations used for pulmonary drug delivery. The liquid formulation is aerosolized most commonly using Capnopen® (Nadiradze et al., 2020a). CapnoPen is a state-of-the-art laparoscopic nebulization device developed in Germany that has been applied in almost all PIPAC studies so far. It can generate aerosols having a median droplet size of nearly 30µm. Moreover, it is capable of aerosolizing a wide array of formulations such as nanoparticles, emulsions, saline solutions, etc (*CapnoPharm GmbH - CapnoPen*, n.d.). A group of researchers utilized computational fluid dynamics or CFD modeling in order to improve IP drug delivery. They examined how the liquid viscosity, flow rate, droplet size, and incorporation of electrostatic fields influenced the uniformity of aerosols in IP drug delivery. The key findings in the study suggested that spatial distribution is favorable when a small droplet size between 1–5 µm was used. If the droplet size is 30 µm, which is in current clinical practice, then a 0.6 mLs^{-1} liquid flow rate provides a favorable aerosol spatial distribution. Moreover, nebulization of liquids having a higher viscosity leads to decreased homogeneity in the distribution of aerosol. The study also suggested that aerosol distribution uniformity is remarkably improved by the incorporation of electrostatic precipitation (Rahimi-Gorji et al., 123 C.E.).

Chapter 5: Efficacy, adverse effects, and other pharmacokinetic data from clinical trials

5.1 Completed clinical trials

There is a record of nine completed clinical trials related to PIPAC and PC in the ClinicalTrials.gov database. The topic of these trials along with the institutes carrying out these trials is summarized in table 2.

Table 2: Completed clinical trials of PIPAC used for Peritoneal Carcinomatosis (ClinicalTrials.gov, n.d.).

Sl.	Topic of study	Study phase/type	Drug name/Treatment	Institute & region
1	Safety and efficacy evaluation of PIPAC in PC of ovarian, gastric, colorectal origin, and primary peritoneal tumors	Phase 1, Phase 2	1. Oxaliplatin 2. Cisplatin & doxorubicin	Candiolo Cancer Institute (Italy)
2	Treatment of PC using PIPAC	Phase 2	1. Oxaliplatin 2. Cisplatin & Doxorubicin	Odense University Hospital (Denmark)
3	Influence of PIPAC on the survival rate of patients who have PC of gastric origin	Comparative non-randomized study	1. PIPAC with systemic chemotherapy 2. Systemic chemotherapy alone	Grenoble Alpes University Hospital (France)
4	Ethical analysis of involvement of industry in PIPAC model development.	Interview	NA	Université de Paris (France)
5	PIPAC for treatment of PC of colorectal origin	Phase 2	Oxaliplation as repetitive ePIPAC (ePIPAC-OX)	Catharina Hospital, St. Antonius Hospital (Netherlands)

6	Cisplatin and Doxorubicin in PIPAC for recurrent ovarian cancer and PC	Phase 1	Cisplatin & Doxorubicin	Ruhr University, Marien Hospital (Germany)
7	PIPAC in Gastric Cancer	Phase 2	Cisplatin & Doxorubicin	Ruhr University of Bochum (Germany)
8	PIPAC Nab-pac in pancreas, stomach, ovarian and breast cancer	Phase 1	Abraxane	Ghent University Hospital (Belgium)
9	Assessment of safety of healthcare professionals in PIPAC procedure	NA	NA	ICM - Cancer Institute of Montpellier (France)

Abbreviations: ePIPAC-OX: Repetitive electrostatic pressurized intraperitoneal aerosol chemotherapy with oxaliplatin, Nab-pac: Albumin bound nanoparticle paclitaxel, NA: Not applicable.

5.2 Efficacy of treatment

The first evidence of the efficacy of PIPAC was obtained in 2014 from a study in which PIPAC was given as compassionate treatment to three end-stage peritoneal carcinomatosis patients. Systemic chemotherapy was previously administered to all the patients. The drugs given with PIPAC were doxorubicin (1.5 mg/m^2) and cisplatin (7.5 mg/m^2). In the trial, the concentration in plasma was low (4.0–6.2 ng/ml) and the local concentration in the peritoneum was high (B4.1 lmol/g). Partial histologic healing was seen in one patient and complete histologic healing was seen in the other two patients. Along with systemic chemotherapy, PIPAC showed synergism (Solass et al., 2014). In another study of 12 patients with PC of pancreaticobiliary origin cisplatin and doxorubicin were given every six weeks in the same dose as the previous study. One patient showed significant tumor regression while four patients showed complete tumor regression which

demonstrated the efficacy of PIPAC (Horvath et al., 2018). In a phase one dose escalation study of cisplatin and doxorubicin in PIPAC, 15 patients who had PC and recurrent ovarian cancer were given 2.3 PIPAC courses on average and examined. 64% of patients who went through two or higher than two PIPAC courses showed tumor regression (C. B. Tempfer et al., 2018). A phase 2 study was conducted on 53 women having PC from recurrent ovarian, peritoneal, or fallopian cancer. After three courses of doxorubicin-cisplatin PIPAC, peritoneal carcinomatosis index and tumor regression improved in 76 percent of patients. Researchers suggested that PIPAC was well endured and efficacious in these patients (C. B. Tempfer et al., 2015). In the case of PIPAC incorporating nanoparticle albumin-based paclitaxel or NAB-PTX, a phase one study was conducted. After observing the dose-response relationship, tumor regression was seen in ⅞ patients with a dose of 140 mg/m^2. A desirable pharmacokinetic characteristic and efficacy were observed with NAB-PTX PIPAC (Ceelen et al., 2022b). Following the application of PIPAC, most research has discovered promising responses in terms of improvement of symptoms (50-91%), histologic response (36-88%), and peritoneal cancer index (65-76%) (Akaishi et al., 2021b). After evaluation of 11 retrospective and 4 prospective cohort studies, 62–88% of patients having PC from ovarian cancer showed a response from treatment with PIPAC when it was given as a third treatment option. The median survival of these patients was 11·0 to 14·1 months. On the other hand, 50% to 91% of gastric cancer patients showed a response with 8·4 to 15·4 months' median survival. Finally, 71–86% of colorectal cancer patients and 67–75% of peritoneal mesothelioma patients showed objective clinical response with PIPAC where median survival was 15·7 months and 27 months respectively (Alyami et al., 2019b). It can be concluded that PIPAC has shown promising efficacy in the treatment of peritoneal carcinomatosis of various origins. However, although several studies have shown positive outcomes of tumor response to PIPAC, a lack of clinical

homogeneity makes interpretation of these results difficult. For example, differences in the presence or absence of concomitant systemic therapy and differences in the primary tumor can make the comparison of efficacy results difficult. Therefore, further standardized studies are needed to define the efficacy of PIPAC in different clinical conditions more accurately. Since most of the studies on PIPAC are up to phase I and phase II clinical trials until now, it is expected that larger phase III trials will help to assess the efficacy of PIPAC further (R. J. Lurvink et al., 2021b).

5.3 Dosage regimen

Several dose-escalation studies have been conducted to estimate the appropriate dosage regimen for PIPAC. In dose-escalation studies of PIPAC, the dose of the selected chemotherapeutic agent is increased in small doses at a time in various groups.

Dose-escalation studies of PIPAC with oxaliplatin:

A phase I dose-escalation study of PIPAC with oxaliplatin (PIPAC-OX) was conducted on 16 patients with a 3+3 dose-escalation method. The patients had PC of gastrointestinal origin and first-line chemotherapy failed in these patients. The applied doses were 45, 60, 90, and 120 mg/m^2. A positive linear relationship was observed between the dose and the highest level of the drug according to pharmacokinetic data. A dose of 120 mg/m^2 was suggested by the researchers for the phase II trial of PIPAC-OX (Kim et al., 2021). Another phase I study determined the pharmacokinetic parameters of PIPAC with oxaliplatin in patients having advanced PC from GI tract cancers. This study included 10 patients who underwent a total of 33 PIPAC courses. This dose-escalation study also utilized a 3+3 design. 90 mg/m^2 was the first dose, which was successively elevated by 50 mg/m^2. At a dose of 90 mg/m^2, there was no presence of dose-limiting

toxicity. However, two dose-limiting toxicity was observed with 140 mg/m^2. Therefore, the recommended dose for oxaliplatin was 90 mg/m^2 (Dumont et al., 2020).

Dose-escalation studies of PIPAC with cisplatin and doxorubicin:

A phase I dose-escalation study of PIPAC with cisplatin and doxorubicin was conducted in women who had recurrent ovarian cancer. A 3+3 dose-escalation method was used. Three cycles of doxorubicin (1.5 mg/m^2) and cisplatin (7.5 mg/m^2) were administered for 4 to 6 weeks with a 20 percent increment in each dose escalation step. The study did not reveal any dose-limiting toxicity. The recommended safe dose for cisplatin was 10.5 mg/m^2 and the recommended safe dose for doxorubicin was 2.1 mg/m^2 (C. B. Tempfer et al., 2018).

Dose-escalation studies of PIPAC with paclitaxel:

Recently, a phase I study has been done on the nanoparticle albumin-based paclitaxel or NAB-PTX for its application as PIPAC. A Bayesian design was applied in this dose-escalation study. NAB-PTX was administered in the dose range of 35-140 mg/m^2. The experiment revealed suitable pharmacokinetic characteristics of NAB-PTX. The maximum tolerated dose or MTD was 140 mg/m^2. The recommended dose by researchers for further phase II trials was 140 mg/m^2. A decreased dose of 112.5 mg/m^2 is recommended for patients having diminished hepatobiliary activity (Ceelen et al., 2022c).

Recommended dosage regimen:

For PC of colorectal origin, a 92 mg/m^2 dose of oxaliplatin in 150 ml dextrose solution is recommended, where m^2 denotes body surface area. Whereas for PC of other origins, the chemotherapeutic drugs cisplatin and doxorubicin are administered with PIPAC. In this case, 7·5 mg/m^2 dose of cisplatin in 150 ml (0·9%) sodium chloride and 1·5 mg/m^2 dose of doxorubicin in 50 ml (0·9%) sodium chloride is usually used. If it is possible, at least three PIPAC cycles are

given in intervals of 6 weeks. The parameters for nebulization are- 30 ml/min flow rate, 1380 kPa pressure, room temperature of 22°C, and 30 minutes duration (Grass et al., 2017).

5.4 Short-term and long-term adverse effects

The adverse effects of oxaliplatin PIPAC have been examined in a phase I study involving 16 patients with PC. Among these patients, adverse events occurred in 37.5% (six) patients. Within one week of treatment with PIPAC, 12.5% of patients reported abdominal pain, and 6.3% of patients reported vomiting, fatigue, or fever. Pancreatitis occurred in two patients at 45 mg/m2 dose and in another patient at 90 mg/m^2 dose (Kim et al., 2021). Another phase I study of oxaliplatin PIPAC has been conducted with 10 patients and 33 PIPAC courses. There were 11 toxicities of grade III and IV severity and 67 adverse effects of grade I and II severity (Dumont et al., 2020). A few severe and some frequent minor adverse effects of oxaliplatin PIPAC has been reported in a phase II study as well. This study involved 20 patients and 59 PIPAC courses. 15% (3 out of 20) of patients showed severe adverse effects including- transient hepatotoxicity, intraperitoneal bleeding, iatrogenic pneumothorax, and abdominal pain. One patient died due to sepsis, which was possibly therapy-related. All patients experienced minor adverse effects. The most frequent minor side effect reported for all patients was abdominal pain. Nausea was also reported by 65% of patients after completion of 39% of procedures (Rovers et al., 2021). In the case of doxorubicin and cisplatin-associated PIPAC, adverse effects were observed in a trial of 15 recurrent ovarian cancer and PC patients. One grade III adverse effect occurred here which was colon perforation. This was due to a surgical complication and the perforation was fixed in that same session. Another patient died after 24 days following PIPAC administration because of advancement in disease. The minor grade I and II adverse effects included fatigue, nausea or

vomiting, abdominal pain, sleep disturbances, diarrhea, and fever. There were no signs of renal, hepatic, hematologic toxicity, neurotoxicity, or alopecia in any of the patients (C. B. Tempfer et al., 2018). A different phase II study evaluated the side effects of doxorubicin followed by cisplatin PIPAC in 53 patients. These patients had recurrent fallopian, ovarian, or peritoneal cancer with PC. Bowel obstruction, trocar hernia, abdominal pain, cystitis with urosepsis, intraoperative bleeding, and hematoma were the grade III adverse effects observed. No fatality occurred in the trial and there was no presence of grade IV toxicities (C. B. Tempfer et al., 2015). In the case of paclitaxel (NAB-PTX) PIPAC, adverse effects were evaluated in 23 patients. 13 of these patients underwent systemic chemotherapy as well. Anemia and hepatotoxicity were the most common toxicities observed. Surgical site problems related to trocars occurred in some patients which included wound dehiscence and infection. There was thrombopenia in a few patients. Neutropenia was found in a patient who was given the highest dose. However, neutropenia and thrombopenia resolved on their own. There was no fatality in the trial (Ceelen et al., 2022c). Finally, it has been reported from initial trials that the usage of PIPAC with systemic chemotherapy does not cause notable renal or hepatotoxicity (Robella et al., 2016). Therefore, early phase I and phase II PIPAC studies have revealed some major adverse effects and some frequent minor adverse effects for different chemotherapeutic drugs. A graphical representation of some of these adverse effects is shown in figure 4. Further trials should focus on minimizing such side effects, especially the severe ones.

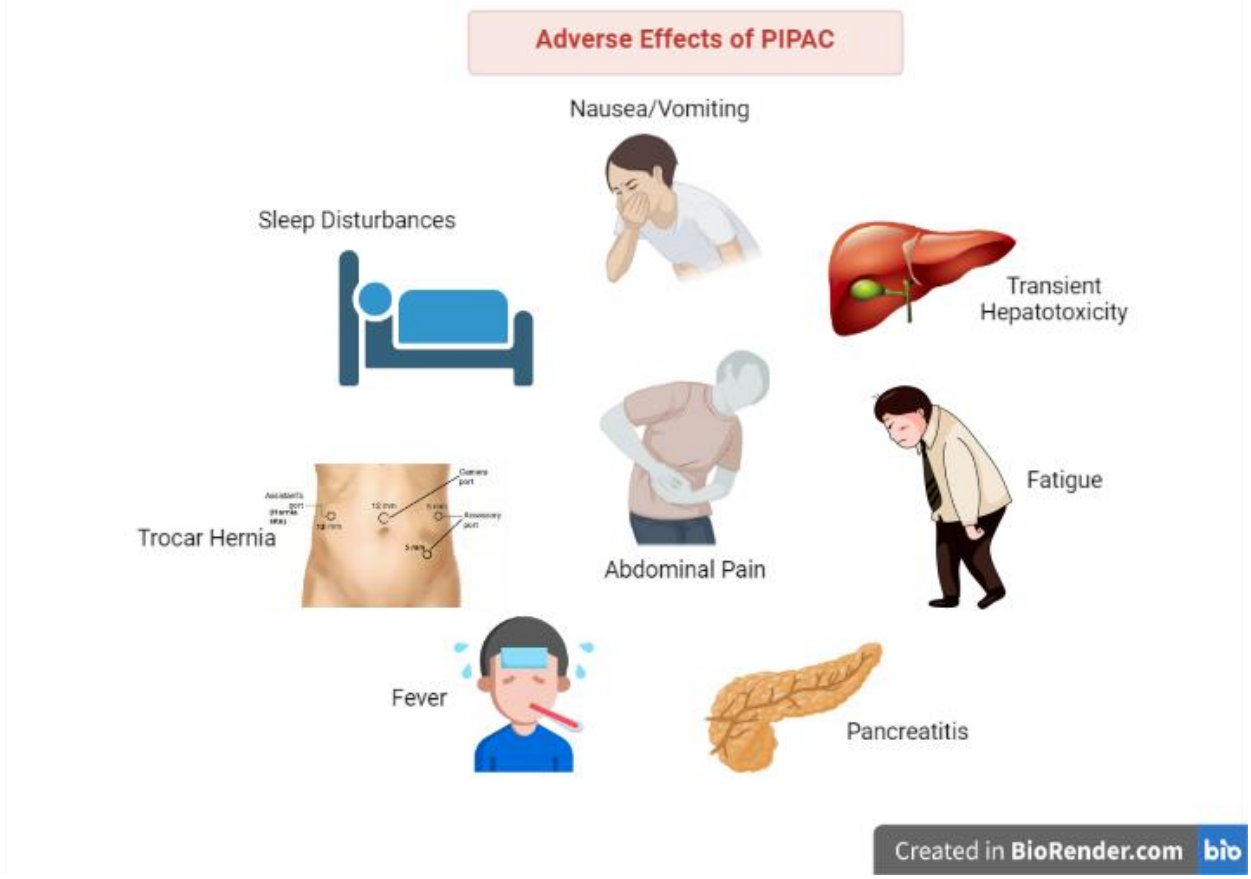

Figure 4: Some adverse effects of PIPAC.

5.5 Quality of life (QOL) following therapy

In palliative care for cancer patients, any treatment should not degrade the existing quality of life (QOL) of the patient, if not make it better. A palliative treatment that stabilizes the quality of life of a seriously ill patient can be considered a positive outcome (Garg et al., 2019). As a palliative treatment, PIPAC has been able to stabilize or upgrade the quality of life of patients with peritoneal carcinomatosis.

In 2015, a German study first presented the QOL after treatment with PIPAC. The study involved 91 end-stage PC patients and 158 PIPAC procedures. Systemic chemotherapy was administered

in 86% of these patients. During the treatment, the researchers used the QLQ30 questionnaire to assess QOL in these patients. It was observed that initially, the global physical score declined moderately from 82% to 75% after the first PIPAC procedure. However, the score improved as much as 89% after the second PIPAC procedure. This result indicates an elevated QOL in patients with advanced PC. Moreover, there was no decline in QOL in terms of gastrointestinal symptoms due to treatment with PIPAC, except for a temporary slight increase in pain scores (Odendahl et al., 2015). Another study reported improved gastrointestinal symptoms and global physical health in patients after PIPAC treatment. This phase II prospective trial also utilized EORTC QLQ30 scores for QOL evaluation. However, results showed that the dyspnoea and pain scores increased during PIPAC treatment. Abdominal pain was reported by all patients in the study (C. B. Tempfer et al., 2015). The same authors reported in another study that appetite, nausea, constipation, and global physical health scores in QLQ-30 improved in their retrospective cohort group (Grass et al., 2017; C. Tempfer et al., 2015). Finally, there has been no report of degradation of cognitive or emotional abilities after treatment with PIPAC. Improvement in nutritional condition has been observed under PIPAC treatment (Oh et al., 2021b). Aside from a few negative effects on quality of life, it can be said that the overall QOL of patients after treatment with PIPAC is stabilized or improved according to the conducted studies.

Chapter 6: Comparison of PIPAC with existing treatment strategies

6.1 Advantages of PIPAC over alternative therapies

PIPAC has several advantages over alternative therapies for PC. Firstly, the current standard of treatment for PC is CRS and HIPEC which require complicated surgical intervention. Mortality and morbidity are also high with these procedures. Whereas the PIPAC procedure is not as invasive as CRS and HIPEC. Moreover, not all patients of PC can go through extensively invasive treatment options. This is why minimally invasive PIPAC can be advantageous for such patients (Leebmann & Piso, 2018). Compared to HIPEC, there is also less chance of chemical bowel perforation in PIPAC (Anwar & Kasi, 2022). Secondly, PIPAC has shown promising results in terms of therapeutic ratio which is the ratio of tissue concentration and dose. Its therapeutic ratio is better compared to systemic chemotherapy, HIPEC, laparoscopic HIPEC, and liquid IP chemotherapy. Thirdly, repeated administration of PIPAC is possible and safe, which is another advantage. Fourthly, biopsies taken during each PIPAC procedure enable the examination of tumor responses to therapy. PIPAC offers several other advantages over conventional therapies. For example, it has the potential to overcome the resistance of peritoneal carcinomatosis patients to chemotherapy. Some patients having PC develop resistance to chemotherapeutic agents. PIPAC helps to overcome such drug resistance possibly due to its delivery of a local high dose in the peritoneum (Nadiradze et al., 2020b). Since there is a poor supply of blood vessels or vascularization in the peritoneum, systemic chemotherapy often shows unsatisfactory results in PC. PIPAC enables the local delivery of chemotherapy in the peritoneum, thus reaching target tissues and lowering systemic concentration (Mohammad et al., 2022).

6.2 Clinical practice guidelines:

In order to establish clinical practice guidelines for PIPAC, experts from the relevant scientific and medical field need to address a wide range of issues.

In October 2019, 49 PIPAC centers took part in a consensus meeting. The panel agreed on 21 out of 33 topics. There were agreements regarding major issues including- incorporating a safety checklist (98%), the usage of PRGS or peritoneal regression grading score (85.7%), ventilation mechanism of operation theater (91.8%), and remote observation (95.9%). There was also debate about some topics such as combining PIPAC with further surgical interventions. There was also a dispute regarding how many biopsies should be performed and from which parts biopsies should be taken after repeated administration of PIPAC. Further discussion and research are necessary to address the issues of disagreement (Hübner et al., 2022). Another consensus was reached between experts in the field regarding the protocols of PIPAC in a consensus meeting in July 2021 in Paris. 22 experts participated in this discussion. The experts had an agreement for all 10 out of 10 questions. 16 out of 22 or 72.7% of experts supported the use of oxaliplatin at a dose of 120mg/m^2 and suggested decreasing the dose to 90 mg/m^2 in the case of frail patients. Combination therapy of oxaliplatin-PIPAC and the cytotoxic drug fluorouracil (5-FU) was recommended by 77.2% of experts. Whereas 20 out of 22 or 90.9% of experts recommended the application of doxorubicin and cisplatin at 2.1 mg/m^2 and 10.5 mg/m^2 doses respectively as a combination therapy. The panel also suggested nab-paclitaxel and mitomycin-C as other alternative drug choices (Sgarbura et al., 2022).

6.3 Electrostatic precipitation PIPAC (ePIPAC):

A recent advancement which is broadening the scopes of PIPAC is electrostatic precipitation PIPAC or ePIPAC. In PIPAC, the distribution of chemotherapy in the peritoneal space can be nonuniform due to the effect of gravity. In ePIPAC, there is the application of electrostatic force which may facilitate resolving such limitations (Gorji et al., 2021). In 2016, ePIPAC was first tested in humans in a study of three patients having peritoneal carcinomatosis of hepatobiliary-pancreatic origin. These patients were administered cisplatin (7.5 mg/m^2) and doxorubicin (1.5 mg/m^2) for 30 minutes. 37 °C temperature and 12 mmHg pressure were applied. An electron-emitting electrode was used to create 7500–9500 V voltage and ≤10 μA current. It was observed that ePIPAC was well tolerated and created a promising tumor response in the patients (M. Reymond et al., 2016). ePIPAC has high technical feasibility. ePIPAC procedure takes less time compared to PIPAC. A higher drug uptake can be achieved with ePIPAC (Kakchekeeva et al., 2016). On the contrary, the quality of life was lowered temporarily in some ePIPAC studies. Moreover, a study showed that ePIPAC caused an elevated systemic level of oxaliplatin which was undesired (R. Lurvink et al., 2020). Therefore, the development of ePIPAC is still at an early stage and there needs to be more research to enhance its application and overcome the challenges.

6.4 Availability of the technology worldwide

A lot of centers which offer HIPEC have also included PIPAC recently. In almost 30 countries worldwide, there are approximately 100 specialized PIPAC centers which administer PIPAC to trial-enrolled patients. A lot of institutions globally are taking preparations to establish their first PIPAC initiative (Teixeira Farinha et al., 2017). A study was conducted to explore the process and challenges faced to introduce PIPAC as a new treatment in Poland. One of the major issues

discovered was that there was insufficient technical and scientific expertise regarding the conduction of PIPAC. Another important problem was obtaining the required technology and equipment for PIPAC. For example, there were difficulties in contacting the manufacturers and suppliers of PIPAC instruments. The study revealed that the problem of insufficient expertise was overcome as they joined workshops and visited PIPAC centers in other countries (Nowacki & Zegarski, 2018). The access to instruments needed for PIPAC can be facilitated by representatives from respective countries. Therefore, PIPAC can be gradually adapted in more countries worldwide by collaborating with other countries in which this new technology is already established. The department of oncology in hospitals of a country can play a key role in introducing this novel technology.

Chapter 7: Future aspects of PIPAC

7.1 Challenges of treatment with PIPAC

Despite the promising results observed with PIPAC, there are several challenges that need to be addressed for successful implementation in clinical practice. In comparison with other dosage forms, PIPAC can increase the risk of the healthcare team being exposed to toxic chemotherapeutic drugs since its dosage form is aerosol. Thus managing this health hazard is a crucial challenge in PIPAC (Solaß et al., 2013). Another challenge arising in this field is the duplication of clinical studies. There have been instances where identical doses of drugs and procedures were used. Such unnecessary duplication patterns can slow down the transition into greater phase three trials (Tate & Torkington, 2020). Another cause of concern is the improper implementation of the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework for PIPAC. This framework helps to define the development stages of new surgical technologies and inventions. According to this framework, all PIPAC trials were supposed to be on record in a public online database such as EudraCT or ClinicalTrials.gov. Only 23 clinical studies have been registered on EudraCT or ClinicalTrials.gov whereas the actual number of published trials on PIPAC is 67. Thus some of the PIPAC centers failed to follow the IDEAL framework (P et al., 2009). The next challenge is that there have been limited studies on the comparison of PIPAC with alternative treatments such as systemic chemotherapy. More research is needed to establish the benefits of PIPAC monotherapy and the combination of PIPAC and other treatments (Alyami et al., 2019c). Another challenge is that there have been some severe adverse events associated with PIPAC reported in some trials. Moreover, a frequent side effect was abdominal pain among others which can negatively impact the quality of life of some patients.

7.2 Approaches to overcome the challenges

Systematic planning and measures should be taken in the future to resolve the challenges in PIPAC. Adequate safety measures must be implemented to eradicate the chances of accidental exposure of healthcare professionals to chemotherapeutic materials during PIPAC procedures. Operating room airflow and design, remote monitoring, safety checklists, safe disposal of toxic substances, etc can help reduce this risk (Oh et al., 2021b). The duplication of similar clinical trials can be avoided by better harmonization of PIPAC centers and researchers. Choosing patients, drug selection, and dose selection should be done in a way to minimize duplication. All new clinical trials must follow the IDEAL framework guidelines and be recorded in the appropriate clinical trial online database. More studies should be conducted to compare the outcomes of PIPAC monotherapy and bidirectional PIPAC combined with systemic chemotherapy. A recent systematic review has pointed out the importance of improving and standardizing the reports on this issue (Ploug et al., 2020). More evidence regarding the long-term efficacy and safety of PIPAC can be obtained once the larger phase III trials are completed. In order to reduce the common side-effects that have been identified with PIPAC, modifications can be made to the different parameters applied during the procedure. For example, ePIPAC has emerged as an addition to the PIPAC technology which may aid in homogenous drug distribution. Modifications can be made in the chemotherapeutic formulation as well such as the use of nanoparticles such as albumin-bound paclitaxel nanoparticles showed higher efficacy in PC than the solvent-based formulation of paclitaxel (Van De Sande et al., 2018). Diminishing the side-effects of PIPAC with such new technologies and inventions may help to improve the quality of life of patients further in the future.

Chapter 8: Conclusion

Peritoneal carcinomatosis is one of the fatal cancers with poor treatment options. It develops through a complex pathophysiology and has strong associations with other cancers. Patients with other types of cancers have a higher risk of developing PC, which can reduce their median survival. From the findings of this study, it is evident that Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC) has excellent potential to treat peritoneal carcinomatosis of different origins. In PIPAC, chemotherapeutic agents are administered using high intraperitoneal pressure in an aerosol dosage form via laparoscopic system. Its procedure requires controlling specific parameters including- pressure, flow rate, temperature, duration, etc. The operating room for PIPAC needs to meet specific design criteria. Pre-operative and anesthesia considerations also need to be considered before the procedure. PIPAC achieves high intraperitoneal drug concentrations with low systemic drug levels. PIPAC has shown promising tumor regression in studies. The most commonly used drugs in PIPAC are oxaliplatin, cisplatin, and doxorubicin with the recommended doses 92 mg/m^2, 7·5 mg/m^2, 1·5 mg/m^2 respectively. Frequent minor and some infrequent major adverse effects were observed for treatment with PIPAC. PIPAC offers several advantages over conventional treatments such as HIPEC, CRS, and systemic chemotherapy. As a minimally invasive technique, PIPAC is considered a good treatment option for patients who are not suitable for CRS and HIPEC. However, research in PIPAC is still in its early phases and some challenges are ahead. These challenges include- duplication of clinical trials, getting access to PIPAC equipment, absence of scientific expertise regarding this technology, lack of studies comparing PIPAC with other therapies, lack of long-term data, etc. Resolving these challenges in the future may allow clinicians of oncology to consider PIPAC as an improved treatment strategy for treating patients with peritoneal carcinomatosis.

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