Doi: 10.5152/TJAR.2019.15493

Original Article
General Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Anaesthesia in a Toxic Environment: Pressurised Intraperitoneal Aerosol Chemotherapy: A Retrospective Analysis

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Cite this article as: Rouche A, Hübner M, Grass F, Pache B, Demartines N, Blanc C. Anaesthesia in a Toxic Environment: Pressurised Intraperitoneal Aerosol Chemotherapy: A Retrospective Analysis. Turk J Anaesthesiol Reanim 2020; 48(4): 273-9.

Abstract

Objective: Pressurised intraperitoneal aerosol chemotherapy (PIPAC) is a new type of intraperitoneal chemotherapy for peritoneal carcinosis via minimally invasive surgery. This technique's specificity is the remote application of the therapy because of the potential risk of exposure to toxic products. The present paper summarises the important aspects of PIPAC and analyses the anaesthetic outcomes.

Methods: This retrospective study included all patients undergoing PIPAC treatment between January 2015 and February 2018. Data on protocol adherence and perioperative anaesthetic complications and postoperative nausea and vomiting (PONV) and pain levels (visual analogue scale 0–10) from recovery room to 72 h were analysed.

Results: The overall analysis included 193 PIPAC procedures on 87 patients. Protocol adherence was high as regards the use of propofol (100%), rocuronium (98%), antiemetic prophylaxis (99%) and lidocaine intravenous (i.v.) (87%). No accidental exposure to chemotherapy occurred during the study period. Of the 87 patients, 6.3% suffered delayed recovery, 58% due to hypothermia and 42% due to excessive sedation or curarisation. In the recovery room, 16% of patients suffered moderate to severe pain, requiring >8 mg of morphine i.v., with average doses of 13.7 mg. Median postoperative pain scores were 1 and 3 at 12 h and 0 and 0 at 72 h at rest and mobilisation, respectively. PONV was observed in <10% of patients during the first 12 h, but in 40% at 72 h.

Conclusion: A dedicated anaesthetic protocol and intraoperative safety checklist facilitates safe, well-tolerated anaesthesia for PIPAC treatments.

Keywords: Adverse effects, doxorubicin, laparoscopy, peritoneal metastases, pressurised intraperitoneal chemotherapy

Introduction

Peritoneal cancer (PC) is a challenging pathology to diagnose and treat. Without therapeutic management, expected survival time is <6 months for PC of colorectal origin or primitive diseases of the peritoneum (1-3). Palliative systemic chemotherapy has a 5-year survival of <15% due to low penetration of the agents and a high incidence of complications. Since 1990, hyperthermic intraperitoneal chemotherapy (HIPEC) in combination with cytoreductive surgery (CRS) has improved outcomes, and the median survival time of patients increased to 22.9 months in a selected cohort of patients (4-6). However, CRS+HIPEC is associated with significant morbidity and mortality rates (42% and 3.8%, respectively), even in specialist referral centres, and quality of life (QoL) is impaired for months after the procedure (4, 7, 8). Therefore, only patients in good general condition can be considered for this treatment. Furthermore, HIPEC has important pharmacokinetic limitations, namely single-dose administration and poor distribution and tissue penetration (9).

Pressurised intraperitoneal aerosol chemotherapy (PIPAC) is a new type of intraperitoneal drug delivery which overcomes some of the above limitations (10). It consists of an intraperitoneal application of vaporised aerosol chemo-

The study was presented as an oral communication at the 11th International Workshop on Peritoneal Surface Malignancy, September 9–11, 2018, Paris and as a poster at the SSAR Congress, November 8, 2018, Interlaken, Switzerland.

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Received: 20.07.2019 Accepted: 27.08.2019
Available Online Date: 26.12.2019

therapy via minimally invasive surgery using a specific nebuliser (CapnoPen®). This approach has been shown to improve distribution and tissue penetration considerably (10-12).

Furthermore, PIPAC can be applied repeatedly, thus increasing the potential to achieve local control of recurrent PC and allowing sequential tumour sampling during laparoscopy. Moreover, chemotherapy doses applied during PIPAC are approximately 10 times smaller than systemic chemotherapy, thus reducing systemic exposure (13).

The present recommendations are for three applications of PIPAC over 3 months. The chemotherapy regimens currently proposed are oxaliplatin alone for colorectal cancer and doxorubicin and cisplatin for PCs of other origins. Platinum agents may induce anaphylactic reactions and can irritate the eyes, skin and airways; they are toxic to the kidneys and bone marrow (14, 15). Doxorubicin provokes mucosal inflammation, leukopenia and dilated cardiomyopathy. Both cytotoxic drugs are carcinogenic to humans (class 2A according to the International Agency for Research on Cancer) (16-19).

Owing to the potential leaks of aerosolised cytostatics, a special safety protocol is needed to reduce exposure risks to healthcare staff. The currently proposed protocol involves the remote administration of chemotherapy, with no direct access to the patient for approximately 30 min. This is particularly challenging for an anaesthesiology team as it requires adaptations to standard protocols for comparable procedures regarding invasiveness and duration, such as laparoscopic cholecystectomy.

Therefore, the aim of the present study was to summarise the important aspects of this particular procedure from the anaesthetic point of view and analyse anaesthetic outcomes.

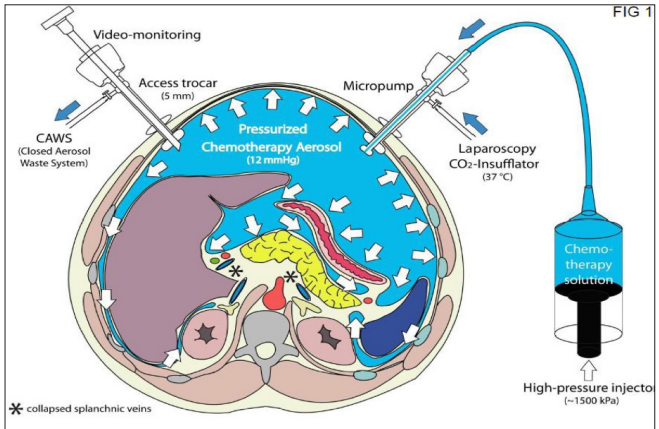

Figure 1. Diagram of pressurised intraperitoneal aerosol chemotherapy. The abdominal cavity is accessed using two balloon trocars, which create a hermetic seal. Liquid chemotherapy is dispersed as an aerosol by using a standard injector and a specific nebuliser (21)

Methods

This retrospective analysis included all consecutive patients undergoing PIPAC at Lausanne University Hospital between January 2015 and February 2018. All patients were discussed at multidisciplinary tumour boards, and typical indications were isolated peritoneal disease in patients not amenable to CRS+HIPEC.

The study was approved by Lausanne University Hospital's Institutional Review Board (no. 2016-00274) and conducted and reported in compliance with the STROBE criteria and registered online (http://www.researchregistry.com; UIN: 4332). All patients were asked for consent to the use of their anonymised clinical data, via a general consent form, as per Swiss law. Patients refusing to sign the form were excluded from the study.

Anaesthetic protocols and an intraoperative safety checklist and procedure were designed in close collaboration with the surgical team before the study started (20). The anaesthetic protocol and safety checklist are provided as an online Appendix 1.

Safety considerations

During the study period, the same surgeon was supported by a dedicated team of anaesthesiologists and instrument technicians for all the PIPAC procedures. Owing to the administration of a carcinogenic chemotherapy, pregnant or breastfeeding women were not allowed to enter the operating room (OR).

Pressurised intraperitoneal aerosol chemotherapy was performed in an OR with a laminar flow, as per safety protocol. Before the vaporisation phase, the surgeon and the entire team run through the safety checklist. During and after the administration phase, healthcare staff must wear a high filtration face mask (FFP3), surgical gown, double nitrile gloves and protective glasses to avoid exposure to the skin and mucosa in case of accidental exposure when entering the OR. With these precautions, entry into the OR due to an anaesthetic problem is allowed if urgently required.

PIPAC procedure

The procedure lasts approximately 90 min and is technically comparable to laparoscopic cholecystectomy (Figure 1). Laparoscopy is performed using a standard pressure of 12 mmHg (CO_2 pneumoperitoneum) using two balloon trocars (21). The first part of the procedure involves an evaluation of the disease extent using the PC index (22). Peritoneal biopsies are obtained, and ascites is removed from the abdominal cavity. Chemotherapy is then vaporised using a high-pressure injector connected to a nebuliser that was de-

veloped specifically for PIPAC. The injector is remote-controlled, allowing the staff to be outside the OR during the administration of intraperitoneal chemotherapy. The drugs are vaporised for 5 min, and then therapeutic CO_2 pneumoperitoneum is maintained for 30 min to allow drug penetration into the tissues. At the end of the procedure, the pneumoperitoneum is exsufflated via the closed aerosol waste system through two sequential microparticle filters into the anaesthetic air waste system.

Anaesthetic considerations

PIPAC patients are given general anaesthesia with standard tracheal intubation. Owing to the patient's inaccessibility during the vaporisation phase, monitoring must be possible from outside the OR to allow remote-controlled drug injection if needed.

Positioning and monitoring techniques

The patient is positioned in the supine position, with legs apart resting on straight pads, allowing the surgeon access between the legs. The left arm is positioned along the body, and the right arm is in abduction at 90° for venous access. A forced air system (Bair Hugger™) is placed over the upper body. In addition to standard anaesthetic monitoring (electrocardiogram, blood pressure, saturation and temperature), depth of anaesthesia is assessed using a bispectral index, and neuromuscular response is closely monitored using a hand accelerometer. These parameters must be available to the anaesthesiologists outside the OR, either through a window or on a second screen. The patient must be kept strictly and continuously immobile during the vaporisation. Two peripheral venous routes are put in place. The first is used for the induction and maintenance of anaesthesia. The second is connected to a long line and is accessible from outside the OR if re-injection is needed.

Before initiating the vaporisation, monitoring, venous access and patient positioning must be reassessed, and the surgical team goes through the operational safety checklist (online Appendix 2).

Sedation and curarisation

Propofol is the preferred choice for the induction and maintenance of anaesthesia, as it reduces postoperative nausea and vomiting (PONV) better than volatile anaesthesia. Furthermore, intravenous (i.v.) anaesthesia enables the use of a closed aerosol waste system for exsufflation of the toxic pneumoperitoneum at the end of the procedure.

Curarisation must last until the end of the procedure to ensure complete patient immobility and constant intra-abdominal pressure with a target post-tetanic count of between 5 and 8–10 measured using an automated accelerometer. Rocuronium is preferred for its ability to be quickly reversed by sugammadex if needed.

Multimodal pain management

Standard analgesia based on a medium-acting opioid (fentanyl) is given to patients for intubation and surgery. A continuous infusion of lidocaine i.v. is initiated at induction (bolus 1.5 mg kg^{-1}) and continued (2 mg kg^{-1} h^{-1}) until departure from the recovery room to reduce opioid use and the side effects of nausea and vomiting and to optimise postoperative analgesia. In addition, patients receive a magnesium sulphate infusion at a rate of 40 mg kg^{-1} over 10 min.

Postoperative analgesia is based on paracetamol, nonsteroidal anti-inflammatory drugs and morphine on demand for the postoperative period.

Prevention of PONV

The combination of general anaesthesia and chemotherapy can potentially amplify PONV. Therefore, patients receive an association of three antiemetic drugs: droperidol and dexamethasone at the beginning of the procedure and ondansetron before waking up and for the postoperative period. In cases of intense PONV, fosaprepitant was selected as a rescue treatment.

Data management

Demographic, surgical and anaesthetic details for all patients were prospectively entered in a computerised, coded database designed specifically for the quality control of the PIPAC cohort. Demographic data included age, sex, body mass index, American Society of Anesthesiologists and cancer origins. Anaesthetic protocol adherence was analysed with regard to the presence of the dedicated anaesthetic team and the protocol's proposed drug usage. Recorded anaesthetic complications included severe arrhythmia, haemodynamic instability, anaphylaxis, mild hypothermia (defined as a temperature from 32.2°C to 35.5°C), delayed recovery (>15 min after the end of surgery), difficult i.v. access (defined as needing more than two attempts) and moderate to severe pain (defined as needing >8 mg of morphine in the recovery room). For the first 74 PIPAC procedures, patients described their pain using a visual analogue scale, and the incidence of PONV was assessed from the recovery room until 72 h and entered in the quality control database.

Statistical analysis

Statistical analysis was performed using Stata Software (v. 14.2; StataCorp, College Station, TX, USA). Continuous variables were presented as mean±standard deviation or median value with range or interquartile range (IQR), as appropriate, depending on the normality of the distribution.

Results

A median of 2 (1–7) PIPAC treatments was performed on our 87 patients, with a total of 193 procedures. The cohort's demographic information is shown in Table 1. The median postoperative length of stay was 2 (IQR 2–3) days.

All surgeries were performed by the same surgeon, whereas anaesthesiologists and nurse anaesthetists from the dedicated team were present at 79% and 55% of procedures, respectively. The overall protocol adherence was high with respect to the use of propofol (100%), rocuronium (98%) and multimodal antiemetic prophylaxis (99%). Lidocaine perfusion was used in 169 (87%) surgical procedures and continued until departure from the recovery room. Sugammadex had to be used in 52 (27%) procedures.

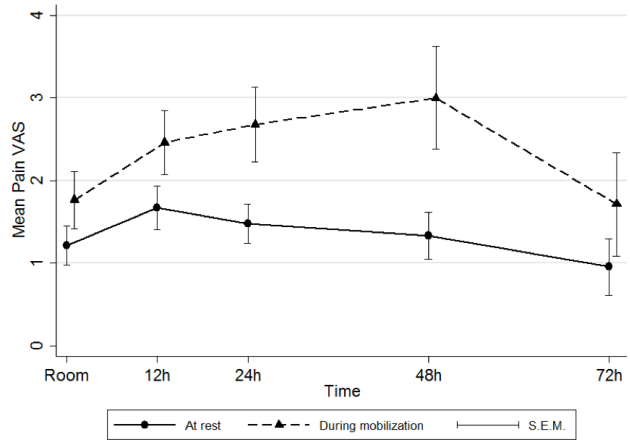

Figure 2. Pain scores at rest and during mobilisation. Evolution of pain scores over time after a PIPAC procedure, at rest and during mobilisation at different time points postoperatively
VAS: visual analogue scale; S.E.M.: standard error of the mean; Room: recovery room

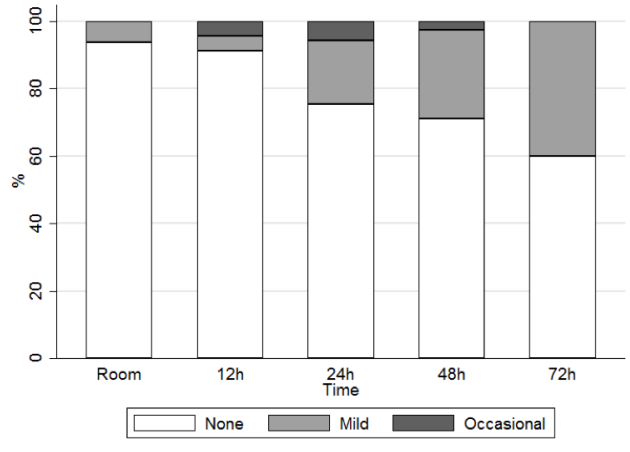

Figure 3. Postoperative nausea and vomiting (PONV). PONV after PIPAC at different time points
Room: recovery room; PIPAC: pressurised intraperitoneal aerosol chemotherapy

Anaesthetic complications occurred in 32 (16.5%) procedures. Twelve (6.3%) patients suffered delayed recovery due to hypothermia (n=7) or excessive sedation or curarisation (n=5). Ten (5.2%) patients had mild hypothermia at the end of the procedure. Other anaesthetic complications were 3 difficult intubations, 4 difficult i.v. accesses and 10 mild haemodynamic instabilities during the laparoscopic phase, requiring low-dose vasopressor treatment.

In the recovery room, moderate to severe pain was documented after 31 (16%) procedures, requiring >8 mg of morphine i.v. and with median doses of 13.7 mg (IQR 8.2–19.2). Median postoperative pain scores were 1 (IQR 0–4) and 3 (IQR 0–4) at 12 h and 0 (IQR 0–2) and 0 (IQR 0–3) at 72 h at rest and mobilisation, respectively (Figure 2). Symptoms of PONV were present in 6.1% of patients in the recovery room and in 40% of the 25 patients who were still in the hospital at 72 h (Figure 3).

No accidental exposure to chemotherapy occurred during the study period. Entry to the OR during the vaporisation phase was necessary <10 times, principally for anaesthetic pump dysfunction.

Table 1. Patient demographics

No. of patients	87
Median age, years (IQR)	63 (55–70)
Sex	
Male	25 (27.8%)
Female	65 (72.2%)
Median BMI, kg m^{-2} (IQR)	23.7 (21.2–26.8)
ASA	
II	57 (65.5%)
III	30 (34.4%)
Aetiology of cancer	
Ovarian	39 (44.8%)
Colorectal	29 (33.3%)
Gastric	8 (9.2%)
Mesothelioma	4 (4.6%)
Other	7 (8.1%)
Median no. of PIPAC procedures (range)	2 (1–7)
Median length of stay, days (IQR, range)	2 (2–3, 1–20)

IQR: interquartile range; BMI: body mass index; ASA: American Society of Anesthesiologists; PIPAC: pressurised intraperitoneal aerosol chemotherapy

Discussion

To the best of our knowledge, this is the first study to analyse the anaesthetic management and complications of patients undergoing PIPAC treatment. This surgical technique is special because the safety drug protocol requires the remote administration of intraperitoneal chemotherapy, limiting access to the patient. By using a dedicated anaesthetic protocol, anaesthesia for PIPAC ensured the safety of patients and healthcare staff, and anaesthetic outcomes were similar to those of comparable procedures.

Pressurised intraperitoneal aerosol chemotherapy is a very new type of treatment, and evidence is so far limited. A first, nine-centre, international survey involved 832 procedures on 349 patients and evaluated the different aspects of PIPAC treatment with respect to surgical methodology. The study demonstrated that the procedures were performed the same way, probably explained by the standardised procedure and the limited number of expert centres (23). A systematic review on PIPAC, published in 2017 by Grass et al. (24), demonstrated that the procedure was safe and well tolerated. Histological response rates for therapy-resistant carcinomatosis of ovarian, colorectal and gastric origins were promising. Furthermore, our group's evaluation of QoL after PIPAC therapy demonstrated no negative impact of the treatment (25).

It has been shown that the safe implementation of PIPAC was possible from the surgical point of view-even with no learning curve-when the existing recommendations and protocols were followed (20). The requirement to be outside the OR and to apply anaesthesia far from the patient is a challenging scenario, but one which has been described previously, for example, in paediatrics with sedation for multiple sessions of radiotherapy (26-28). For the PIPAC procedure, anaesthesia must be given in a potentially toxic environment involving cytotoxic drugs. Although no emanations of cytotoxic agents were detected during experimental procedures and no air contamination was detectable at the surgeon's and anaesthesiologist's workstations (29), strict protocols, a safety checklist and a dedicated team are mandatory for the safe execution of this procedure, including following recommendations on the manipulation of cytotoxic drugs, as for HIPEC procedures (30).

Adherence to the anaesthetic protocol described above was high, despite the staff turnover inherent in a teaching institution. However, a senior anaesthesiologist and referent nurse anaesthetist were available on site, in the event of a problem, and the anaesthetic protocol and safety checklist were available on the department's intranet. This underscores the importance of homogenous pathways in maintaining standardisation regardless of staffing changes.

The overall severity of surgical complications was mild and has already been described by our group. We recorded no micro-pump injector disconnections or accidental vaporisation into the OR air during our series.

By using the recommended protocol, not one major anaesthetic complication was observed in 193 procedures. Hypothermia occurred mainly at the beginning of the study due to the initial technical problems with the laparoscopic-gas heater and/or late positioning of the forced air system and late prevention of hypothermia during anaesthetic induction and installation. However, peripheral venous access was challenging as most patients had few accessible veins due to multiple lines of upfront systemic chemotherapy. Other minor anaesthetic problems, such as haemodynamic instability, difficult intubation and delayed recovery due to excess sedation or curarisation, are inherent to all anaesthetic procedures in a teaching hospital and are not related to PIPAC procedures in particular.

Lidocaine i.v. was added to optimise pain management, but this occurred after the start of our study programme, thus explaining the 87% adherence rate. Pain scores were low thanks to a multimodal analgesic approach based on paracetamol and nonsteroidal anti-inflammatory drugs, and they were similar to those patients undergoing laparoscopic cholecystectomy (31). Only 26 (13.6%) procedures resulted in patients requiring morphine i.v. in the recovery room. With regard to the 40% of patients presenting with PONV at 72 h, only complicated and very frail patients had a hospital length of stay that long, thus explaining this high incidence of PONV.

Conclusion

The anaesthetic management of patients undergoing PIPAC procedures can be performed safely by following the recommendations within a standardised pathway. Subtle adaptations of standard protocols are necessary to adjust to the requirements of the safety protocol, which includes remote administration. Despite this, the anaesthetic management and clinical outcomes of this procedure were comparable with operations of similar invasiveness and duration, such as laparoscopic cholecystectomy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Lausanne University Hospital's Institutional Review Board - Pr. Patrick Francioli (2016-00274).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.H.; Design – A.R., M.H., C.B.; Supervision – A.R., M.H., F.G., N.D., C.B.; Resources – N.D., C.B.; Materials – A.R., B.P.; Data Collection and/or Processing – A.R., B.P., F.G.; Analysis and/or Interpretation – A.R., B.P., F.G.; Literature Search – A.R.; Writing Manuscript – A.R.; Critical Review – A.R., M.H., F.G., B.P., N.D., C.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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