

Cytoreductive surgery and hyperthermic intraoperative chemotherapy is better with open or closed abdomen? Analysis of clinical outcomes

Claudio Ghermandi,¹ Lucia Cipolat,¹ Matteo Martignani,¹ Luca Ansaloni,² Federico Coccolini,² Salomone Di Saverio,³ Belinda De Simone,⁴ Massimo Sartelli,⁵ Fausto Catena⁴

¹Department of Anesthesiology and Reanimation, St. Orsola-Malpighi Hospital, Bologna; ²Department of General and Emergency Surgery, Papa Giovanni XXIII Hospital, Bergamo; ³Department of General Surgery, Maggiore Hospital of Bologna, Bologna; ⁴Department of Emergency and Trauma Surgery, University Hospital of Parma, Parma; ⁵Department of Emergency and General Surgery, Macerata's Hospital, Macerata, Italy

Abstract

The aim was to investigate and analyze clinical outcomes in patients submitted to hyperthermic intraoperative chemotherapy (HIPEC) with open and closed technique.

This is a retrospective analysis of data about 30 patients submitted to HIPEC with open coliseum technique-group 1 and closed technique-group 2 between may 2014 and may 2015. Clinical data about intra-operative monitoring of these patients during hyperthermic chemoperfusion were matched and compared. Statistical analysis was made by SPSS program.

No statistical significant difference was found in the modification of cardiac frequency (P=0.136), of the median arterial pressure (P=0.128), in central venous pressure (P=0.384), cardiac output (P=0.092), and in Stroke Volume Variation (P=0.815) between

the 2 groups. Recovery time in the Intensive Care Unit was 5±3 days for group 1 and 5±2 days for group 2.

Recovery time was 17±6 days for group 1 and 20±11 days for group 2.

There are no data confirming better outcomes of HIPEC with open or closed technique. An experienced operating team is required to decrease morbidity and mortality rate.

Introduction

The improved knowledge of physiopathological changes due to surgical stress, the development of anesthesia and intensive care techniques have allowed for a more aggressive course of treatment in patients before considered inoperable and terminally ill. This holds true in the oncological field, allowing for more radical responses in care.¹⁻³

Cytoreductive surgery (CRS) and hyperthermic intraoperative chemotherapy (HIPEC), first developed in the 1990s, has become an important therapeutic option for selected patients with peritoneal surface malignancies. Aim of this approach is complete elimination of malignant tumor to increase disease free survival and overall survival of patients affected by advanced neoplastic disease.⁴

CRS and HIPEC fall into the high-risk category of abdominal surgery due to their long operating time and significant loss of liquids, blood, plasma, and proteins. Every patients candidate to CRS and HIPEC have to be carefully evaluated and selected before to be submitted to different phases of HIPEC with its own potential surgical risk.⁵⁻⁷

The cytoreduction phase involves the isolation and removal of the parietal peritoneum, visceral peritoneum, and the debulking of tumor mass with multi visceral resection. Furthermore, cytoreduction surgery requires a substantial reshuffling of the circulatory and microcirculatory distribution and consequently alteration to the hydro-electrical and acid-base equilibrium.⁸

The chemohyperthermia phase, lasting about 90 min (60-120 min), consists of continuous cycling infusion of chemotherapeutics ranging from 40° to 42°C. The infusion is carried out by an external circuit that heats and distributes the chemotherapeutics at a speed of 600-1000 ml/min, to guarantee a temperature of approximately 41°C in whole peritoneal cavity.

Significant peripheral vasodilation, caused by hyperthermia, results in a series of systemic repercussions that vary depending on the perfusion technique implemented.

Correspondence: Belinda De Simone, Department of Emergency and Trauma Surgery, University Hospital of Parma, via Gramsci 15, 43100 Parma, Italy.
E-mail: desimone.belinda@gmail.com

Key words: Hyperthermic intraoperative chemotherapy; cytoreductive surgery; pain control; fluid therapy; coliseum technique; closed abdomen technique.

Contributions: CG, LC, MM designed the study; CG collected data and wrote the manuscript; FC revised data and statistical analysis; BDS revised the final manuscript. All the authors read and approved the manuscript.

Conflict of interest: the authors declare no conflict of interest.

Received for publication: 24 October 2016.
Revision received: 31 January 2017.
Accepted for publication: 3 February 2017.

©Copyright C. Ghermandi et al., 2017
Licensee PAGEPress, Italy
Journal of Peritoneum (and other serosal surfaces) 2017; 2:43
doi:10.4081/joper.2017.43

This article is distributed under the terms of the Creative Commons Attribution Noncommercial License (by-nc 4.0) which permits any non-commercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Generally, the procedure is performed through a median laparotomy, providing exposure for a complete meticulous exploration for peritoneal deposits followed by peritoneal and organ resection.

The peritoneal route of chemotherapy is based on the peritoneal plasma partition concept that allows a high concentration of the chemotherapy to be in direct contact with cancerous cells with minimal systemic absorption and side effects. The most commonly used chemotherapeutic agents are mitomycin-c, oxaliplatin, irinotecan and cisplatin. The addition of heat to the chemotherapy potentiates the activity of some chemotherapeutic agents and increase diffusion of the chemotherapeutic agents between the cells.

Intra-operative chemo-hyperthermia can be administered with different techniques: abdominal wall can be left open or closed during the HIPEC therapy period.

In the open coliseum technique, the abdominal wall is elevated to create a funnel to accommodate the heated chemotherapy that circulates through inflow and outflow lines attached to a pump and heating unit. This technique provides that HIPEC is completed prior to the closure of the abdomen cavity. Lifting the edges of the surgical wound upwards and suspending them under traction by threads from a retractor positioned above the abdomen facilitates approach to the peritoneal cavity, optimizes exposure of intra-abdominal organs.

In the closed method, the skin is temporary closed after placing the inflow and outflow tubing through separated incisions. In the laparoscopic approach, the abdominal cavity is filled with the HIPEC solution that circulates using a pump with a heating unit, through laparoscopic incisions.

During the reconstruction phase, surgeon re-establishes the physiological anatomy of abdomen, and anesthetist restores normal volume and temperature.

The aim of this study is to investigate and analyze clinical outcomes in patients submitted to CS and HIPEC.

Materials and Methods

We carried out a retrospective observational study involving 30 patients submitted to CS and HIPEC in the Department of Surgery of St. Orsola-Malpighi Hospital (Bologna, Italy) between may 2012 and may 2013. We divided patients into 2 groups: Group 1, consisting of 15 patients underwent open-abdomen HIPEC (coliseum technique) and Group 2, consisting of 15 patients underwent close-abdomen HIPEC.

Detailed anesthesiologic preoperative evaluation of every patient was made before surgery. This included also an informed consent, signed by the patient, in which an anesthesiologist is listed as responsible for administering pre-operative medication.

General anesthesia was administered by opioids, halothane, sleep inducing and muscle relaxation drugs. To better control intra-operative and postoperative pain, epidural analgesia was administered by thoracic catheter.⁹⁻¹⁵ In Table 1 we summarized advantages of thoracic epidural anesthesia.

To ensure a close monitoring of the patient's vital parameters a standard system of Electrocardiography, capnometer, pulse oxymeter was used associated to FloTrac/Vigileo® technology, to check cardiac index (CI), cardiac output (CO), and stroke volume variation (SVV).¹⁶

Naso-gastric tube and double-lumen bladder catheter with urinometer were positioned after induction of general anesthesia. Thermal regulation was assured by ZERO HEAT FLUX TECHNOLOGY (3M®).¹⁷

Statistical analysis was made by SPSS IBM Statistics program.

Results

Group 1 has a mean age of 50 years (± 8.7), ASA 2/3, mean BMI 24.4 kg/m² (± 2); all the patients of this group underwent open-abdomen HIPEC with Coliseum Technique.

Group 2 has a mean age of 54.8 years (± 13.4), ASA 2/3, mean BMI 23 kg/m² (± 3.9) underwent close-abdomen HIPEC.

Neoplastic diseases affected our population study was summarized in Table 2.

Surgical time was 650 \pm 128 min for group 1 and 637 \pm 71 minutes for group 2.

Hemodynamic stability was monitored in both groups during the chemo-perfusion phase. No statistical significant difference was found in the modification of cardiac frequency (P=0.136), variation of the median arterial pressure (P=0.128), changes in central venous pressure (P=0.384), CO (P=0.092), and in SVV (P=0.815) between the 2 groups.

No catecholamines were administered in our patients. Volumetric and fluid filling was done by crystalloid perfusion at an average speed of 12/15 mL/kg/h in group 1 and 8/12 mL/kg/h in group 2. Perfusion speed was modulated by a continuous administration of diuretics to ensure an hourly diuresis of 0.8-1.5 mL/kg/h.

On average, 1513 \pm 966 mL of concentrated homologous red blood cells, 1076 \pm 746 mL of fresh, frozen plasma and 513 \pm 255 mL of 20% albumin was administered in group 1.

An average of 1496 \pm 875 mL of concentrated homologous red blood cells, 1020 \pm 527 mL of fresh, frozen plasma, and 310 \pm 145 mL of 20% albumin was administered in group 2.

Adverse events were classified according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).¹⁸ Adverse events Grade ½ was found in 22% of patients; adverse events of Grade 3 was found in 8% of patients, requiring further surgery or recovery in the Intensive Care Unit (ICU).

Mean length hospital stay in ICU was 5 \pm 3 days for group 1 and 5 \pm 2 days for group 2.

Mean length hospital stay was 17 \pm 6 days for group 1 and 20 \pm 11 days for group 2.

Table 1. Advantages of thoracic epidural analgesia.

Inferior use of analgesic opioids
Inferior use of halogenic anesthesia
Less arrhythmia incidence
Less bleeding
Excellent post-operative pain management

Table 2. Neoplastic disease of our population study.

Tumor	Group 1	Group 2
Ovarian	10	8
Colon	3	4
Mesotelioma	1	1
Pseudomixoma	-	2
Sarcoma	1	0

Discussion and Conclusions

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has become an important therapeutic option for selected patients with peritoneal surface malignancies. This aggressive multimodality treatment is complex, not only regarding surgical technique, but also regarding anesthesia.

Actually there is no consensus about perfusional protocol for patients submitted to CRS and HIPEC with open or closed technique.

There are no data confirming better outcomes of HIPEC with open or closed technique.

Our data does not provide substantial support for one method over the other.

In our experience there is a small difference in the endo-abdominal temperature, between closed and open technique. The closed technique results in a faster increase in central temperature that does not interfere with the chemo-perfusion procedure.

In regards to the possible dispersion and vaporization of various types of antineoplastic agents during the chemo-perfusion phase, contamination of personnel, taking appropriate clothing and protection is improbable^{19,20} even if one must always consider the words of Favier who wrote: *There will be always doubts, and these should benefit those concerned through a continual search for ways to minimize contact by adapting procedures.*²¹

This approach to advanced neoplastic disease with peritoneal carcinomatosis requires advanced anesthesia administration and an experienced operating team.²² Anesthetic management importantly contributes to the containment of the perioperative complications of HIPEC. Only with a *dedicated team* of surgeons and anesthesiologists with adequate learning curve,²³ careful to fluid exchange, hematic and protein loss, we can decrease peri- and post-operative complications and morbidity rate.

References

- Boyle P, Ferlay J. Cancer incidence and mortality in Europe 2004. *Ann Oncol* 2005;16:481-8.
- D. Baratti, S. Kasamura, M. Deraco M. The Fifth International Workshop on Peritoneal Surface Malignancy (Milan, Italy, December 4-6, 2006): methodology of disease-specific consensus. *J Surg Oncol* 2008;98:258-62.
- Deraco M, Santoro N, Carraro O, et al. Peritoneal carcinomatosis: features of dissemination. *Review. Tumori* 1999;85:1-5.
- Sommariva A, Pilati P, Rossi CR. Cyto-reductive surgery combined with hyperthermic intra-peritoneal chemotherapy for peritoneal surface malignancies: current treatment and results. *Cancer Treat Rev* 2012;38:258-68.
- Glehen O, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. *Lancet Oncol* 2004;5:219-28.
- Kusamura S, Dominique E, Baratti D, et al. Drugs, carrier solutions and temperature in hyperthermic intraperitoneal chemotherapy. *J Surg Oncol* 2008;98:247-52.
- Grocott W, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcome in adults. *Anesth Analg* 2005;100:1093-106.
- Raft J, Parisot M, Marchal F, et al. Meistelman Impact of the hyperthermic intraperitoneal chemotherapy on the fluid-electrolytes changes and on the acid-base balance. *Ann Fr Anesth Reanim* 2010;29:676-81.
- Ali M, Winter DC, Hanly AM, et al. Prospective, randomized, controlled trial of thoracic epidural or patient controlled opiate analgesia on perioperative quality of life. *Br J Anaesth* 2010;104:292-7.
- Marret E, Remy C, Bonnet F. Postoperative Pain Forum Group. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg* 2007;94:665-73.
- Desgranges F-P, Steghens A, Rosay H, et al. Piriou Analgésie péridurale pour le traitement chirurgical des carcinomes péritonéales: une pratique à risque? *Ann Franç Anesth Réanimat* 2012;31:53-9.
- Guay J. The benefit of adding epidural analgesia to general anesthesia: a metaanalysis. *J Anesth* 2006;20:335-40.
- Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of post-operative epidural analgesia: a meta-analysis. *JAMA* 2003;290:2455-63.
- Guay J. The effect of neuraxial blocks on surgical blood loss and blood transfusion requirements: a meta-analysis. *J Clin Anesth* 2006;18:124-8.
- Jørgensen H, Wetterslev J, Miniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens for postop GI paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev* 2000;(4):CD001893.
- Moonesinghe SR, Mythen MG, Das P, et al. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery. *Qual Syst Rev Anesthesiol* 2013;119:959-81.
- Teunissen LP, Klewer J, de Haan A, et al. Non-invasive continuous core temperature measurement by zero heat flux. *Physiol Meas* 2011;32:559-70.
- Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176-81.
- Schmid K, Boettcher MI, Pelz JO, et al. Investigations on safety of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with Mitomycin C. *Eur J Surg Oncol* 2006;32:1222-5.
- Esquivel J, Sugarbaker PH, Helm CW. Techniques of delivering hyperthermic intraperitoneal chemotherapy. In: C. W. Helm and R. P. Edwards, eds. *Current clinical oncology: intraperitoneal cancer therapy*. Totowa, NJ: Humana Press Inc., 2007.
- Favier B, Latour JF. Exposition des préparateurs et des infirmières res aux cytotoxiques. *Revue de la littérature. Lyon Pharmaceutique* 2001;51:82-107.
- Kavanagh M, Ouellet JF. Comité de l'Evolution des Pratiques en Oncologie. Clinical practice guideline on peritoneal carcinomatosis treatment using surgical cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy. *Bull Cancer* 2006;93:867-74.
- González-Bayón L, González-Moreno S, Ortega-Pérez G. Safety considerations for operating room personnel during hyperthermic intraoperative intraperitoneal chemotherapy perfusion. *Eur J Surg Oncol* 2006;32:619-24.