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RESEARCH ARTICLE

Goal-directed therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: a prospective observational study

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Abstract

Background Cytoreductive surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in peritoneal carcinomatosis treatment causes significant hemodynamic, metabolic, and hematological alterations. Studies on the anesthetic intraoperative management are heterogeneous and scarce. There is a great heterogeneity in the anesthetic management of CRS and HIPEC. The aim of this study is to analyze perioperative hemodynamic goal-directed management and to evaluate the complications arisen until the seventh postoperative day.

Methods Prospective, observational study of all CRS and HIPEC patients from March 2014 to May 2017. Hemodynamic and clinical parameters were registered during surgery and the first 3 postoperative days. We correlated intraoperative data with the postoperative course until the seventh day.

Results A total of 92 patients were included in the study (age 58.5 ± 10.9 years, 47% colorectal carcinoma, and 38% ovarian carcinoma). Peritoneal Carcinomatosis Index (PCI) (median and ranges) was 10 [0–39]. Cardiac Index (CI) 3.15 $l/min^{-1}/m^{-2}$ [1.79–5.60]) and Systolic Volume Variation (SVV) (10% [3%–17%]) remained within the values of normality in all surgery phases. A large difference was observed between the minimum and maximum ranges of fluid therapy administered (median 9.8 ml/kg/h [5.3–24.3]), showing a great interindividual variation in the fluids requirement. A direct relationship was observed between PCI and surgery duration, fluid therapy, and intraoperative transfusion percentage ($p < 0.02$).

Conclusions There is a great variability in the intraoperative fluid therapy needs of the patients. SVV monitoring makes it possible to adjust the fluid therapy needs in each surgery phase. The use of a hemodynamic goal-directed anesthetic protocol in CRS and HIPEC enables to individually adjust the fluid therapy, avoiding over-hydration and ensuring hemodynamic stability in all surgery phases.

Keywords Peritoneal carcinomatosis · HIPEC · Anesthesia · Goal-directed therapy

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Introduction

Cytoreductive surgery (CRS) along with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in peritoneal carcinomatosis (PC) treatment causes significant hemodynamic, metabolic, and hematological alterations [1], proportional to the cytoreductive phase aggressiveness, the temperature during HIPEC, and surgery duration (6–12 h). Peritonectomies, multiple visceral resections, and temperature control in all surgery phases are some of the specific characteristics of this procedure.

The perioperative management of all these alterations poses an anesthetic challenge that requires the establishment of strategies to maintain an adequate normothermia, normovolemia, and tissue perfusion.

A great disparity is observed in the perioperative management of these patients [2]. Matters in controversy include optimal monitoring, fluid therapy, renal protection, vasoactive drugs (VD) use, epidural anesthesia, extubation criteria, as well as the prevention and treatment of hematological and metabolic alterations.

In the last years, 6 prospective studies [3–8] and one randomized clinical trial [9] have been published. The scarce data on the anesthetic management of CRS and HIPEC contrast with the numerous studies with a surgical and oncological approach. In addition, the patients' and methods' heterogeneity is one of the problems in CRS and HIPEC research.

One of the discrepancies in CRS and HIPEC perioperative management regards to the quantity of fluid therapy. Minimally invasive cardiac output (CO) monitoring and dynamic parameters such as the stroke volume variation (SVV) make it possible to individually adjust fluid therapy to the patient's needs and to apply a goal-directed therapy (GDT) based on hemodynamic values. However, data regarding the GDT impact on the results improvement are contradictory [9–11], partly due to the difficulty in isolating an intraoperative measure from the multiple factors that interact in the perioperative process.

The aim of this prospective study was to evaluate the application of an anesthetic protocol based on hemodynamic GDT in CRS and HIPEC. The evolution of the hemodynamic, metabolic, and hematological parameters during the intraoperative period and the first 72 postoperative hours was analyzed, to correlate intraoperative variables with the postoperative course until the seventh day.

Materials and methods

The Multidisciplinary Peritoneal Carcinomatosis Program was introduced in Son Espases University Hospital in January 2014. Inclusion criteria were patients with PC from colorectal cancer, peritoneal pseudomyxoma, ovarian cancer, gastric cancer, peritoneal mesothelioma, age less than 80 years, a good general status (American Society of Anesthesiologists score—ASA I–II, a normal healthy patient o a patient with mild systemic disease, Eastern Cooperative Oncology Group score—ECOG 0–1, patient fully active, able to carry on all pre-disease performance without restriction o restricted only in physically strenuous activity), absence of extraabdominal dissemination and possibility of a complete cytoreductive surgery. Exclusion criteria were unresectability or absence of PC. All candidates were referred to the Multidisciplinary Peritoneal Carcinomatosis Team for further discussion.

The study was approved by the Clinical Investigation Ethical Committee of the Balearic Islands Government (Palma de Mallorca, Balearic Islands, Spain) with number IB 2381/14. The protocol procedures were designed in compliance with the clinical research recommendations of the Declaration of Helsinki.

All participants were informed about the research protocol before giving their written consent to participate in the study.

All patients undergoing CRS and HIPEC from March 2014 to May 2017 were included prospectively in the study, excluding a total of 23 patients who did not undergo HIPEC (17 due to unresectability and 6 due to absence of PC).

An anesthetic protocol based on general anesthesia with propofol or sevoflurane, combined with epidural analgesia and a hemodynamic GDT, was applied to all patients.

The anesthetic protocol included the complete monitoring of ventilation, anesthetic depth, and neuromuscular relaxation; non-invasive hemodynamic monitoring (FloTrac-Vigileo® Edwards Lifesciences S.L. 4.0); fluid therapy and VD use according to dynamic parameters (SVV); evaluation of tissue perfusion analytical parameters; maintenance of diuresis at 0.5 ml/kg/h and of temperature in every surgery phase; and, finally, the application of extubation criteria in the operating theater. The core body temperature was measured with a nasopharyngeal and a bladder thermometer. During the postoperative period in the recovery room, epidural anesthesia and non-invasive hemodynamic monitoring if needed were continued, and fluid therapy was adjusted to maintain an adequate tissue perfusion and to obtain a neutral or preferably negative hydric balance. CRS phase objectives are presented in Table 1.

The hemodynamic and clinical parameters at surgery start, in 3 CRS phases, (C1 at start of CRS, C2 at the half of CRS, and C3 at the end of CRS) and 3 HIPEC phases (H_1 at minute 15, H_2 at minute 30, and H_3 at minute 60), as well as during the first 3 postoperative days, were recorded. The complication follow-up was carried out until the seventh postoperative day.

Table 1 Cytoreductive surgery phase objectives

Cytoreductive surgery phase objectives		
Diuresis		0.5–1 ml/kg/h
Nasopharyngeal temperature		36 °C
Epidural		Levobupivacaine 0.25% 8–10 ml/h
MAP		60–80 mm Hg
CVP		> 5 cm H_2O
pH		>7.35
pH		< 7.35 → improve perfusion
pH		< 7.15–7.20 → ↑ perfusion + sodium B
Lactate		< 2 mmol/l
Serum calcium		Ca^{++} < 4.0 mg/dl → [Cl Ca 10% (0.5–1 g)]
Serum magnesium		Mg^{++} < 1.8 mg/dl → [magnesium S (1.5–3 g)]
$SvcO_2$		> 75% < 85%
Δ v-a CO_2		< 6–7
SVV		10%–13%
IC		≥ 2.5 L/min/m^2
Fluid therapy	Crystalloids (balanced solution)	Plasmalyte®
10–12 ml/Kg/h (initially)	Crystalloids bolus SVV > 13%	250–500 ml
	Synthetic colloids	HES 6%, max 20 ml/Kg (by bleeding)
	Albumin < 35 g/l	Albumin 5%, max 20 ml/Kg
Vasoactive drugs	SVV < 10%	Noradrenaline: CI ≥ 2.5 L/min/m^2
	(+ MAP < 60 mmHg)	Dobutamine: CI < 2.5 L/min/m^2
Algorithm	Clinical + Analytical signs of hypoperfusion	
	+ SVV > 13% → 250–500 ml plasmalyte®	
	+ SVV < 10% + CI ≥ 2.5 L/min/m^2 → noradrenaline	
	+ SVV < 10% + CI ≤ 2.5 L/min/m^2 → dobutamine	

MAP mean arterial pressure, *CVP* central venous pressure sodium B: sodium bicarbonate, *ClCA* calcium chloride magnesium S: magnesium sulphate, $SvcO_2$ central venous oxygen saturation, $\Delta v–aCO_2$ veno-arterial variation of CO_2, *SVV* systolic volume variation, *CI* cardiac index, *HES* hydroxyethyl starch

Epidemiological and clinical data including age, gender, body mass index, primary cancer type, comorbidity, cytostatic type, surgery duration, peritoneal carcinomatosis index (PCI), cytoreduction completeness (CC), organs removed and postoperative complications were also recorded. Complete cytoreduction was defined as no visible nodules at the end of surgery (CC-0) or residual nodules with diameter less than 2.5 mm (CC-1).

HIPEC was performed with an open abdomen/coliseum technique, using 1.25% glucose peritoneal dialysis solution for perfusion. We used mitomycin C (30 mg/m^2) or oxaliplatin (450 mg/m^2) for colon and appendiceal tumors, while paclitaxel (60 mg/m^2/2 L of solution) was used for ovarian tumors and cisplatin (75 mg/m^2) in mesothelioma and gastric cancer.

Statistical analysis

All statistical analyses were performed using the statistical package SPSS statistics 18.0 (SPSS Inc, Chicago, Illinois). Continuous descriptive data were expressed as mean (±SD), median and quartiles ($Q1$–$Q3$), or range. The normality and homogeneity of the sample were confirmed by the Kolmogorov–Smirnov test. Categorical data are given as frequencies and proportions. Between-group differences were assessed using the paired Student's *t* test. To assess correlations among variables, the Pearson or Spearman's rho correlation tests were used as appropriate. Significance was tested at the 5% level of statistical significance ($p < 0.05$).

Results

The study included 92 patients with a mean age of 58.5 years (± 10.9), of which 62% were women. All patients were ASA PS 1 o 2 and ECOG 0 o 1. The tumor origin was colorectal 47%, ovarian 38%, appendix 7%, mesothelioma 3%, peritoneal pseudomyxoma 2%, and others 3%. The anesthetic protocol was applied in 100% of the cases. The peritoneal cancer index (PCI) was (median

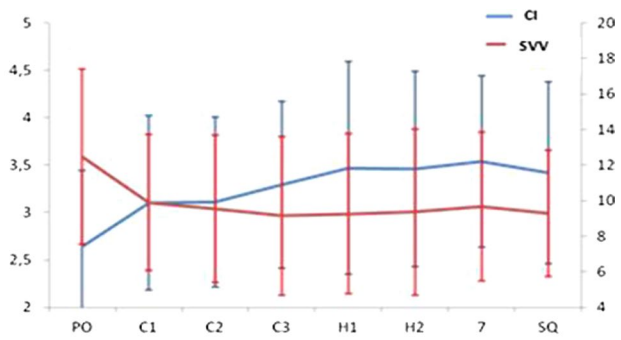
range) 10 [0–39], the average of the resected organ was 3.4 [0–7], and in 98% of the patients, a completeness of cytoreduction was achieved (CC 0/1). Table 2 summarizes the main intraoperative data. Epidural anesthesia was used in all patients less than one due to technical impossibility.

Cardiac index (CI) (median, ranges, and interquartile range—IQR, 3.15 l/min^{-1}/m^{-2}, [1.79–5.60], [2.7–3.7]) and SVV (10%, [3%–17%], [8–11.43]) remained within the values of normality in all surgery phases, with SVV presenting a great interindividual variation. CI increased from the beginning of the intervention until leaving the operating room (OR) ($r = 0.343$, $p = 0.001$). Heart rate (HR), with a median ranges of 79 [39–140] beats per minute, significantly increased during HIPEC ($p = 0.000$). Figure 1 shows the evolution of hemodynamic parameters and temperature.

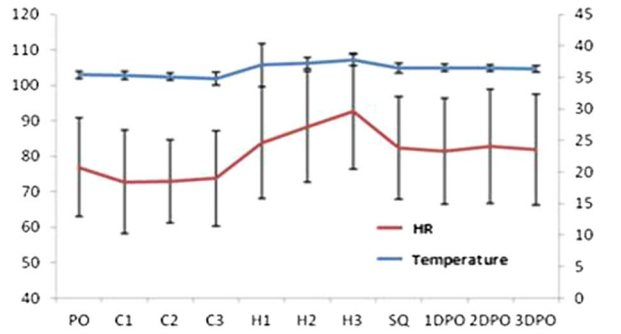
Median nasopharyngeal temperature was 35.2 °C [33.7–36.2] during CRS and 37.2 °C [33.2–39.8] during HIPEC. At the time of leaving the OR, median temperature was 36.2 °C [33.8–37.5]. No correlation was proven between temperature increase during HIPEC and CI values ($r = 0.025$, $p = 0.986$). At the end of HIPEC, nasopharyngeal temperature was correlated with heart rate increase ($r = 0.518$, $p = 0.000$).

A large difference was also observed between the minimum and maximum ranges of fluid therapy administered (median 9.8 ml/kg/h [5.3–24.3]).

Registered pH values decreased from 7.38 [7.26–7.50] at the beginning of surgery to 7.30 [7.14–7.57] during HIPEC,



Evolution and Interindividual Variation of the cardiac index (CI) and the Stroke Volume Variation (SVV)



Evolution and Interindividual Variation of the heart rate (HR) and temperature

Fig. 1 Evolution of CI, SVV, heart rate, and temperature

Table 2 Intraoperative data

Intraoperative data	
No. of patients	92
Epidural analgesia, no. (%)	91 (99%)
Intraoperative fluid rate (mean range)	9.8 ml/Kg/h [5.3–24.3]
Cardiac index (mean range)	3.15 L min^{-1}m^{-2} [1.79–5.60]
Systolic volume variation (SVV)	10% [3–17]
Intraoperative noradrenaline, No. (%)	31 (34%)
Postoperative noradrenaline, No. (%)	3 (14%)
Nasopharyngeal HIPEC temperature (mean range)	37.2 °C [33.2–39.8]
Urine output (mean range)	1.3 ml/Kg/h [0.8–4.1]
Cytostatic No. (%)	Paclitaxel 34 (37%)
	Oxaliplatin 30 (33%)
	Mitomycin 24 (26%)
	Cisplatin 4 (4%)
Intraoperative estimated blood loss (mean range)	500 ml [0–4000]
Intraoperative blood transfusion, No. (%)	28 (30%)
Anastomosis (mean range)	1.1/Patient
Visceral resections (mean range)	3.3/patient
Extubation in the operating room, No. (%)	80 (87%)
Operative time CRS (mean range)	377.5 min [105–670]
Total operating time (mean range)	642.5 min [415–1125]

increasing at the end of surgery to 7.32 [7.19–7.45]. Lactate values increased during HIPEC up to 3.10 mmol/L [0.80–7.50] and normalized without treatment during the first postoperative day (Fig. 2).

Hyperglycemia 396 mg/dl [379–426] was observed during HIPEC despite insulin perfusion to the initial 12 patients group, in which cytostatic (oxaliplatin) was administered in a 5% glucose solution. After changing to 1.25% glucose peritoneal dialysis for perfusion solution, glycemia during HIPEC decreased to 202 mg/dl [135.3–514.5] without requiring routine insulin administration (Fig. 2).

Median values of international normalized ratio (INR) stayed below 1.26 during all phases and normalized at the third postoperative day without requiring blood products' administration. Maximum values were 2.47 during the CRS phase and 1.85 on the third postoperative day. Median platelet count stayed within the normality range, 184 [69–615] $\times 10^9$ L (median and ranges), with maximum decrease on the second postoperative day (Fig. 3).

Transfusions during surgery were needed for 30% of the patients, with an average of 2 red blood cells' concentrates per patient. Patients with hemoglobin (Hb) values below or equal to 9 gr/dl presented a significant increase of the transfusion rate (83% vs 27%, $p=0.0141$). No significant differences were registered for patients with Hb values above 9 gr/dl.

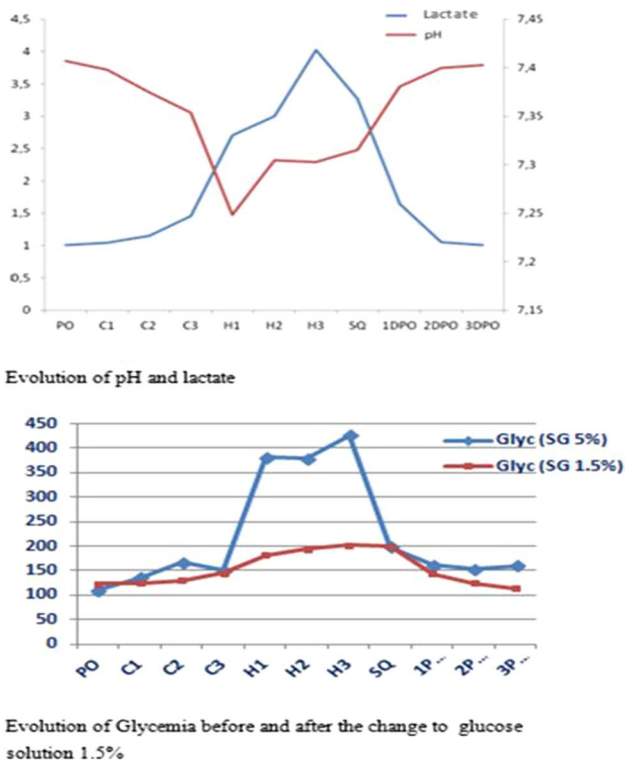


Fig. 2 Evolution of pH, lactate, and glycemia

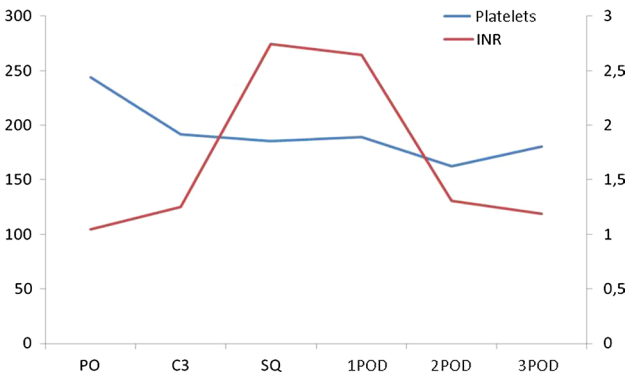


Fig. 3 Evolution of international normalized ratio (INR) and platelet count

The variables' correlation analysis showed a direct and significant relationship between PCI and surgery duration, fluid therapy, and intraoperative transfusion percentage ($r=0.650$, $r=0.601$, $r=0.242$, respectively, $p<0.02$).

Grouping patients by PCI (55% PCI > 10 and 45% PCI < 10) showed no significant correlation between PCI and the extubation in OR rate or the complications percentage until the seventh postoperative day. Patients with PCI > 10 presented a greater incidence of blood transfusion ($r=0.226$, $p=0.030$).

C-reactive protein (CRP) values showed a direct relationship with PCI ($r=0.333$, $p=0.001$) and an inversely proportional relationship with the albumin value on the third postoperative day ($r=-0.481$, $p=0.000$). CRP/albumin quotient increased to 1.7 ± 9.07 on the third postoperative day.

The 12 patients not undergoing extubation in OR received more fluid therapy ($p=0.008$) and noradrenaline ($p=0.009$) and presented more complications ($r=0.298$, $p=0.04$), but no differences were observed in surgery duration or PCI.

Patients receiving an intraoperative fluid therapy above 14 ml/kg/h (13% 12/92) presented 50% of severe complications [12] with a percentage of 33% of postoperative mechanical ventilation.

Among complications registered during the follow-up until the seventh postoperative day, 26% were classified as severe [12]. Most frequent complications were respiratory failure (11%) and pleural effusion (8%) with need of thoracocentesis (Table 3). Fifty diaphragmatic peritonectomies and 14 diaphragmatic resections were performed. This group of patients presented four respiratory complications (4%), two pleural effusion, and two respiratory insufficiencies.

The reintervention rate was 3.3% and postoperative mechanical ventilation more than 24 h, 16.3%.

Table 3 Postoperative complications

Complications	Type	Percentage (No.)
Mild–moderate (Clavien–Dindo[42] I–II)	Neutropenia 6	6% (6)
	Coagulopathy 5	5% (5)
	Mild renal failure 3	3% (3)
19% (18/92)	Respiratory infection 2	2% (2)
	Central line infection 1	1% (1)
	Confusional syndrome 1	1% (1)
Severe (Clavien–Dindo III–IV)	Respiratory insufficiency 10	11% (10)
	Pleural effusion 7	8% (7)
	Intraabdominal infection 4	4% (4)
26% (24/92)	Toxic pneumonitis 1	1% (1)
Mortality	Mesenteric thrombosis 1	1% (1)
Hospital stay (days)		18.3 [7–110]
Critical care stay (days)		4.6 [2–70]

Discussion

In this prospective study on the application of a monitoring and GDT anesthetic protocol, we observed a great interindividual variation in the fluids' requirement. SVV monitoring [10] has enabled us to predict fluid therapy or VD needs in every surgery phase, individually adapting the administration for each patient and thus contributing to the hemodynamic stability observed in this series. The registered 34% use of intraoperative noradrenaline, in contrast to other studies with figures between 50 and 100% [8, 13, 14], may be due to the indication of hemodynamic goal-directed VD. The absence of a hyperdynamic state in the HIPEC phase, as described in other series [7, 8, 15], may be due to the normovolemia at HIPEC beginning and matches the observations of other GDT studies [3, 4, 16]. Standardization of a hemodynamic goal-targeted anesthetic management may contribute to avoid the over-hydration caused by fluid therapy fixed rules and to VD titration.

A survey on intraoperative management carried out in 29 European HIPEC centers [17] registered volume replacement patterns between 10 and 15 ml/kg/h, with a mean of 1–1.8 l/h. In all studies, the fluid therapy type was based on different proportions of crystalloids and colloids and on a systematic or on-demand use of albumin. However, these papers were published before the restriction applied to hydroxyethyl starch. Therefore, new fluid therapy protocols will have to be adapted to the restriction of synthetic colloids, thus probably increasing the use of human albumin.

According to the most recent survey on the current clinical practice of hospitals in different perioperative areas of CRS and HIPEC [18], 90% of centers use minimally invasive CO monitoring. This figure contrasts with the 45% registered in 2012 survey by Bell et al. [17]. Dynamic parameters, like SVV, are better predictors of fluid responsiveness than classical static parameters such as blood pressure, heart rate, or central venous pressure. This monitoring makes it possible to apply a goal-directed fluid therapy, which seems to decrease major complications in CRS and HIPEC patients, according to the clinical trial of Colantonio et al. [9]. However, the patients' groups of this study are not homogeneous, with a higher ovarian cancer proportion, PCI and visceral resections in the control group. Today, and due to its normalized use in CRS and HIPEC, it would be difficult to carry out a clinical trial without using minimally invasive CO monitoring for the control group. The hemodynamic treatment based on GDT has replaced the previous recommendations such as maintaining a fluid therapy of 12–15 ml/Kg/h or using prophylactic noradrenaline or dopexamine.

The reported use of intraoperative epidural analgesia is 72% in the survey by Bell et al. [17] and 100% in the survey by Morales et al. [18], although none of them describes the type or dosage of continuous infusion nor the use of bolus. According to our data, the 99% use of perioperative epidural analgesia has made it possible to decrease the intraoperative opiates dosage and has contributed to perform extubation in OR of 87% of patients. Epidural analgesia has been proven to be a safe practice in CRS and HIPEC, with an excellent postoperative analgesia [19]. Coagulation alterations during the postoperative period are self-limited and seldom imply a delay in catheter removal [5]. The association between the use of continuous intraoperative epidural and a greater administration of fluids or vasoactive drugs in major abdominal surgery is controversial [20, 21]. In our case, both, the median fluid therapy (9.8 ml/kg/h [5.3–24.3]) and the use of noradrenaline (34%), are lower than in most of the published series [13, 17].

Despite active heating methods (forced air-warming blankets and warmed intravenous fluids), hypothermia (< 36 °C) is registered in the CRS phase. This could be reduced with preoperative and during anesthetic preparation heating. During HIPEC, we abandoned the systematic use of cooling methods, applied in the first cases, and actually, we individualize its application. This resulted in maximal temperatures below 39.8 °C, with a mean value of 37.2 °C.

According to other studies [4], a self-limited metabolic acidosis occurs during the HIPEC phase. Reducing glucose in the cytostatic solution from 5% to 1.25% eliminated the need of using insulin perfusion to control hyperglycemia in HIPEC [22]. Registered coagulation alterations normalized in mostly all patients from the third postoperative day, without requiring blood products' administration.

Renal failure incidence, defined as a ≥ 1.5-fold increase over basal creatinine, occurred in 3% of the patients and was mild and self-limited. HIPEC-associated acute kidney injury (AKI) incidence is described between 0 and 18.6%, with a great variability in the definition criteria [23]. Cisplatin use is associated with a greater AKI risk [24], between

3.7 and 5.8% depending on the series. The nephroprotective measures used are based on preoperative hydration and the administration of neutralizing substances. However, there is a low evidence level [25] of their efficacy based on clinical observations and cases series.

Today and following the 2013 recommendations for AKI prevention by the Kidney Disease: Improving Global Outcomes Work Group [26], there is a trend to abandon from using formerly applied renal protection measures such as the prophylactic administration of furosemide and dopamine or the forced diuresis of 200–300 ml/h. These measures, which were based on scarce evidence, are also being discarded in the light of numerous studies with results showing a lack of correlation between fluid therapy, diuresis, and AKI incidence [7, 13, 16, 23, 27].

PCI was correlated with surgery duration, fluid therapy, intraoperative transfusion percentage, and CRP values. In line with other studies [28], we did not find any relationship between PCI and postoperative complications. Other factors such as comorbidity, preoperative symptoms, and previous resections are being described as predictors of major complications. Inverse correlation between CRP and albumin in CRS and HIPEC patients could be a predictor index for complications and, therefore, a subject of future studies.

Major morbidity (26%) and mortality (1%) results of the present study are comparable to those described in other series [29] (30%–57% and 2.3%–3%, respectively), although our follow-up period covered only the first 7 postoperative days and constitutes a limitation of this prospective study.

The following are the main differences of this anesthetic protocol with other published protocols [3, 13].

- Individualized hemodynamic goal-targeted fluid therapy.
- Intraoperative general/epidural combined anesthesia, with intraoperative opioid savings.
- VD (noradrenaline) use according to dynamic parameters and not to prophylactic use or from a fixed volume of fluid therapy.
- Non-application of "renal protection" rules: pre-HIPEC systematic furosemide administration, pre-HIPEC forced diuresis at 100 ml/h or dopamine.
- Colloids usage (hydroxyethyl starch) only for blood loss substitution.
- No prophylactic plasma transfusion.
- Criteria for extubation in OR, independent from surgery duration.

Conclusions

A great heterogeneity can be found in the anesthetic management of CRS and HIPEC. A literature review presents few studies, mostly retrospective and with a reduced number of patients, so there is no evidence on optimal anesthetic management.

There is a great variability in the intraoperative fluid therapy needs of the patients.

The use of a monitoring and hemodynamic GDT anesthetic protocol in CRS and HIPEC makes it possible to individually adjust the fluid therapy and VD use, avoiding over-hydration and ensuring hemodynamic stability in all surgery phases.

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Authors contribution NEP, AFR, and GGR were responsible for conceptualizing and designing the study, collecting, analyzing, and interpreting the data, and drafting the manuscript. MVR and DFG contributed to the conception and design of the study and to the revision of the manuscript. LCMF, RMS, and JJSS were responsible for the critical revision of the intellectual content of the manuscript. STG contributed to the analysis and interpretation of the data. All authors gave their approval on the final version for publication.

Compliance with ethical standards

Conflict of interest Drs. Neus Esteve Pérez, Ana Ferrer-Robles, Germán Gómez-Romero, David Fabián-Gonzalez, Mateo Verd-Rodriguez, Luis Carlos Mora-Fernández, Rafael Morales-Soriano, Juan José Segura-Sampedro, and Silvia Tejada-Gavela have no conflicts of interest or financial ties to disclose.

Ethical Standard The study was approved by the Clinical Investigation Ethical Committee of the Balearic Islands Government (Palma de Mallorca, Balearic Islands, Spain) with number IB 2381/14. The protocol procedures were designed in compliance with the clinical research recommendations of the 1964 Declaration of Helsinki.

Research involving human participants or animals This article does not contain any study with animals performed by any of the authors.

Informed consent All participants were informed about the research protocol before giving their written consent to participate in the study.

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