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Security and efficiency of a closed-system, turbulent-flow circuit for hyperthermic intraperitoneal chemotherapy after cytoreductive ovarian surgery: perioperative outputs

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Abstract

Objective To present physiologic intraoperative data and immediate postoperative outcomes of patients diagnosed with epithelial ovarian cancer submitted to cytoreductive surgery and hyperthermic peritoneal intraoperative chemotherapy (HIPEC) with a closed-circuit, turbulent-flow system.

Materials and methods A closed-circuit system with CO_2 turbulent flow was used for paclitaxel HIPEC during 60 min for patients diagnosed with stage II or higher and recurrent epithelial ovarian cancer. Perioperative hemodynamic and metabolic statuses were followed, as well as physiologic recovery during the first 12 postoperative hours. A non-parametric statistical analysis was performed.

Results At the end of the hyperthermia phase, temperature was 37.7 ± 0.6 °C, heart rate 88 ± 19 bpm, cardiac index 2.8 ± 0.5 L min^{-1} m^{-2}, stroke volume variation 14.6 ± 3.6 % and extravascular lung water 8.7 ± 1.9 mL kg^{-1}. No hyperdynamic status was recorded. The length of stay in the ICU was 2½ days, and 12.7 ± 7 days in hospital. Average postoperative intubation time was 11.7 ± 17.4 h. At the ICU admission time, glucose, lactic acid and hemoglobin were the only values out of range, but close to normal. SOFA median was 3 at admission and 0 the following day.

Conclusion A turbulent-flow, closed-circuit use for hyperthermic peritoneal intraoperative chemotherapy resulted in no hyperdynamic response or coagulopathy, had good tolerance and promoted early physiologic recovery.

Keywords Epithelial ovarian cancer · Hyperthermic intraperitoneal chemotherapy · Intraoperative outputs · Postoperative outcomes

Introduction

When epithelial ovarian cancer (EOC) is diagnosed, it is already disseminated across the peritoneal surface in 70–80 % of the patients, 50 % has lymphatic infiltration and 13 % has metastatic disease [1]. Front-line treatment includes cytoreductive surgery (CRS) and adjuvant chemotherapy, usually with carboplatin. The amount of residual tumoral tissue after CRS is key to determine overall survival (OS) of EOC patients. Intraoperative hyperthermia might be synergistic with chemotherapy in the peritoneal cavity [2], enhancing tumor cell killing capacity. Based on the uncontrolled series [3], the use of hyperthermic intraperitoneal chemotherapy (HIPEC) makes sense for advanced and recurrent EOC for the time being, but definitive data from randomized clinical trials [4] remain to be seen. The classic open-abdomen *coliseum* technique for HIPEC is currently being substituted in most centers for closed-circuit techniques. The latter has various theoretical advantages: increased ability to quickly achieve and maintain hyperthermia, increased pressure of the chemotherapeutic-containing solution upon the peritoneal surfaces,

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more stable patient temperature and physiologic response, minimal heat loss and minimized exposure of the operating room staff to chemotherapy drugs [5, 6]. We report our HIPEC pilot series testing security and efficiency of a newly designed closed-circuit turbulent-flow device and compare our early outcomes with other available series. Once the performance of the device is checked by this pilot series, a randomized trial focused on long-term oncologic outcomes will be started in the near future (EUDRA-CT 2011-006319-69).

Materials and methods

Women diagnosed with EOC class II and higher as well as recurrent EOC were submitted to CRS and HIPEC at the Hospital General Universitario de Ciudad Real from November 15 2011 to January 31 2013, fulfilling a pilot program previous to a randomized clinical trial to be started latter on, during 2013 (EUDRA-CT 2011-006319-69). This pilot program was approved by the ethics committee. All patients gave written consent before they were included. The standard surgical procedure included a cytoreductive phase: hysterectomy and bilateral oophorectomy (except patients who already had a previous incomplete surgery and patients suffering a relapsed episode of their ovarian cancer disease), lymphadenectomy of the pelvic and para-aaortic areas and resection of peritoneal implants. Once the cytoreductive surgery was completed, the HIPEC phase took place using paclitaxel [7, 8] (175 mg m^{-2}) at 42–43 °C during 60 min. Paclitaxel molecule has a safe and effective profile for HIPEC use: high molecular weight (853.9 Dalton), responsible for the low systemic absorption rate and high peritoneal concentration [9]. Bowel and liver resection, in case indicated, was done before the HIPEC phase but the intestinal anastomoses were completed afterwards to preserve it from any possible deleterious effect of HIPEC.

All patients received a balanced general anesthetic. A thoracic epidural placed in awake patients at T7–T8 level was considered for perioperative management in some patients per anesthesiologist criteria. Only three anesthesiologists were involved in this series. All patients were monitored with a Pulse Contour Cardiac Output PiCCO (Pulsion® Medical Systems AG, Munich, Germany) device inserted in the radial artery [10]. Blood temperature was monitored by the in-line PiCCO probe (tip situated in the superior cava) in addition to an esophageal probe (GE Healthcare Finland Oy, Helsinki, Finland). A norepinephrine infusion was started at low doses with a *damage-control* intention to ameliorate the rate of IV fluids that were infused whenever such rate was deemed excessive (>1/2 L h^{-1}) and systemic vascular resistance (SVR) was not above normal. Dobutamine was

used in case Cardiac Index (CI) was lower than 2.0 L min^{-1} m^{-2} and unresponsive to fluid resuscitation. Signs of under-resuscitation for our goal-directed fluid management [11] were Stroke Volume Variation SVV >13 % as main criteria and secondly Global end-diastolic volume (GEDVI) <650 mL m^{-2}. Gloves, goggles and a respiratory mask filter (FFP3D type, DACH™ Schutzbekleidung GmbH & Co. KG, Bietigheim, Germany) were used by operating room personnel during the HIPEC phase. The patients were transported to the surgical ICU and intubated after the surgery was completed. Complications noticed during the ICU stay or latter on in the ward were classified using a previously validated system [Criteria NCICT for adverse events (CTCAE) version 4.0. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-014_QuickReference_8.5x11.pdf. Accessed March, 2013]. This classification is disclosed as follows. Grade 1, *Mild*; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2, *Moderate*; minimal, local or noninvasive intervention indicated; limiting age-appropriate Activities of Daily Living. Grade 3, *Severe* or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living. Grade 4, *Life-threatening* consequences; urgent intervention indicated. The patients were scheduled to receive 6 follow-up cycles of IV carboplatin (AUC 6) and paclitaxel at 175 mg m^{-2} postoperatively.

We used for our patients a newly designed closed circuit, the *Combat PRS*™ (Peritoneum Recirculation System, Galmaz Biotech, Madrid, Spain) (Figs. 1 and 2). This model combines three parallel recirculation circuits: two for fluids and one for CO_2. Pressures are maintained within a 12–15 mm Hg range, flow rate at 2,000–2,400 mL min^{-1} and temperature 41–43 °C. CO_2 recirculation generates an intra-abdominal turbulent flow that facilitates a homogeneous distribution of the perfusion solution across the peritoneal surfaces. The entrance multiperforated tube was placed under the left diaphragm, running between the descending colon and the abdominal wall, crossing the pelvis and up to the right diaphragm between the ascending colon and the abdominal wall. On the contrary, the exit drain was placed in the pelvis, running up to the right diaphragm, towards the left side and down to the pelvis. CO_2 was inflated through a tube positioned behind the mesenteric root to elevate and separate the intestinal loops. CO_2 was passively exited at the abdominal cupola with a corrugate tube, closing the system with no leaks. Fluid temperature was tested at the entrance and exit tubes. The usual volume necessary to fill-up the circuit was 4 ± 0.5 L. The solution contained glucose 75.7 mmol L$^{-.1}$, sodium 132 mmol L^{-1}, calcium 1.75 mmol L^{-1}, Magnesium 0.25 mmol L^{-1}, chloride 101 mmol L^{-1}, bicarbonate 25 mmol L^{-1}, sorbitol

Fig. 1 Two pumps of peristaltic inflow/outflow (2,400 mL min^{-1}). CO_2 exchanger. Heat exchanger
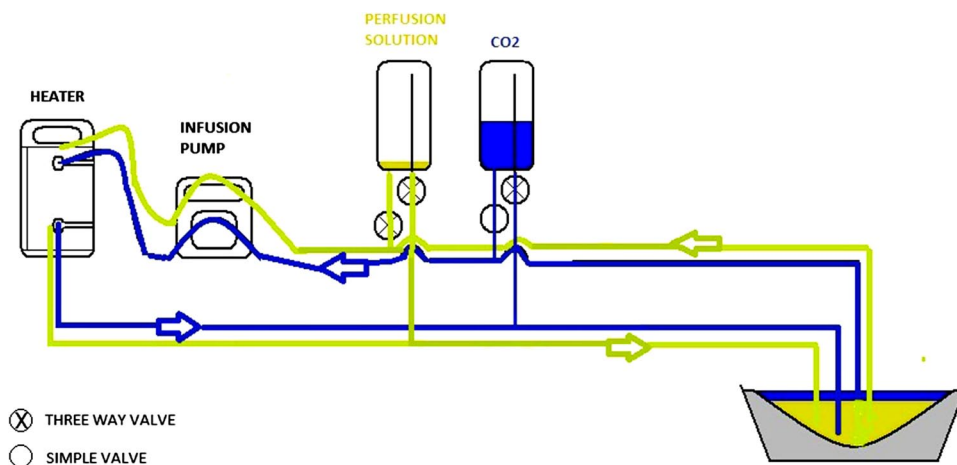
Fig. 2 Roller pump for intraperitoneal hyperthermic chemotherapy

10 mmol L^{-1}; osmolarity 345 mOsm L^{-1}; and pH 7.4. The skin and subcutaneous tissue were closed with a running suture for the HIPEC phase. A circuit and peritoneal cavity *lavage* was done after HIPEC and the in–out volume difference was calculated to figure out residual volume, transperitoneal fluid absorption and circuit spillage to estimate room staff contamination risk. Bowel anastomoses were completed after the HIPEC phase.

Literature searches in MEDLINE, LILACS, Google Scholar and Cochrane Library Databases were done using "HIPEC" and "postoperative outcomes", "HIPEC" and "complications", "HIPEC" and "hemodynamics". We obtained 81 results. Twenty were repeated. After abstract review, 13 articles were ruled out due to unrelated contents. After full review of the articles, 21 were discarded due to non-usable information. We included 27 articles in our review.

Preoperative, intraoperative and postoperative data (hemodynamic and laboratory outcomes and clinical complications) were collected prospectively and entered into a computerized database. The principal variables were time to extubation and SOFA (Sequential Organ Failure Assessment) score. Qualitative outcomes were presented as median and 25–75th ‰ and quantitative outcomes as mean and standard deviation. The Wilcoxon signed rank sum test (coupled comparison) or Friedman test (serial comparison) was used to compare paired variables. Spearman's *rho* was used to establish correlations of temperature, time to extubation, Simplified Acute Physiology Score (SAPS), Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA. Significance was accepted with *p* values 0.05 or lower.

Results

Fifteen patients were submitted to cytoreductive surgery and HIPEC with a closed-circuit, turbulent-flow system. Age, past medical history, histological features and surgery extent are depicted in Table 1. An intraoperative norepinephrine infusion was used in 7 cases. Dobutamine was never used. The average total procedure time (anesthetic and surgical time altogether) was 492 ± 54 min. Total IV fluid infusion rate was 10 mL kg^{-1} h^{-1}. We used a colloid–crystalloid ratio of 1:4. Intraoperative urine output was 113 ± 50 mL h^{-1}. A low thoracic epidural was placed in 9 patients. Temperature, IV fluids, blood products use, metabolic status and hemodynamic changes related to the HIPEC phase are shown in Table 2. Blood temperature was correlated with GEDVI ($\rho = 0.69$; $p = 0.004$) by the end of the HIPEC phase. The necessary volume to fill-up the circuit was 4.2 ± 0.4 L. The in–out volume difference ranged 465–1,220 ml (Fig. 3).

The physiological status at the arrival to the ICU appears in Table 3. The length of stay (LOS) in the ICU was consistently 60 ± 5 h (2½ days) and 12.7 ± 7 days in hospital.

Table 1 Patient characteristics and surgery extent

Age (mean ± SD)	58.8 ± 14.9
Past medical history [n (%)]	
High blood pressure	7 (46.6)
Non insulin-dependent diabetes mellitus	3 (20)
Dislipemia	2 (13.3)
Obese	1 (6.6)
Breast cancer	2 (13.3)
Neoadjuvancy	6 (40)
Incomplete previous pelvic surgery	2 (13.3)
Recurrent ovarian cancer	4 (26.6)
ASA classification [n (%)]	
2	12 (80)
3	3 (20)
Pathology [n (%)]	
Serous	10 (66.6)
Mucinous	2 (13.3)
Endometrioid	1 (6.6)
Clear cells	1 (6.6)
Other	1 (6.6)
FIGO	
Stage IIa	1 (6.6)
Stage IIc	2 (13.3)
Stage IIIB	1 (6.6)
Stage IIIC	8 (53.3)
Stage IV	3 (20.0)
Peritoneal cancer index (mean ± SD)	10.4 ± 7
Surgery extent [n (%)]	
Hysterectomy and bilateral oophorectomy	15 (100)
Pelvic and paraaortic lymphadenectomy	15 (100)
Omentectomy	9 (60.0)
Bowel resection	5 (33.3)
Gastric	1
Small bowel	1
Left hemicolectomy and primary anastomosis	2
Right hemicolectomy and primary anastomosis	1
Subdiaphragmatic implant resection	5 (33.3)
Appendectomy	5 (33.3)
Hepatic resection	1 (6.6)
Splenectomy	1 (6.6)
Completeness cytoreduction score [n (%)]	
No visible residual tumor, CC0	12 (80)
<1 cm residual tumor, CC1	3 (20)

ASA American Society of Anesthesiology, *FIGO* International Federation of Gynecology and Obstetrics

APACHE II at ICU admission correlated with SVV at the end of HIPEC ($\rho = 0.7$; $p = 0.003$). Median intubation time was 6 h. Only three cases remained intubated more than 12 h and only one patient more than 24 h (actually, 72 h). The changes in the physiologic status of our

population and SOFA score 12 h after admission (day 2) are shown in Table 4; the score on day 2 correlated with low prothrombin time by the end of the HIPEC phase ($\rho = -0.62$; $p = 0.04$). Urine output was 107 ± 44 mL h^{-1} during those 12 h, down to 86 ± 32 mL h^{-1} the following day ($p = 0.01$). The first day volume balance in the ICU was $2,166 \pm 956$ mL, down to $936 \pm 1,745$ mL ($p = 0.03$) the next day.

We had 18 grade 1 complications in 12 patients (morbidity 80 %), which included nausea and vomiting ($n = 1$), metabolic acidosis ($n = 4$), pleural effusion ($n = 1$), neutropenia ($n = 4$), low platetet count ($n = 2$), arterial ischemia ($n = 1$), ileus ($n = 2$), delirium ($n = 1$) and hematuria ($n = 1$); 15 grade 2 complications in 7 patients (morbidity 46.7 %), which included reintubation ($n = 1$), soft tissue collection ($n = 1$), deep vein thrombosis ($n = 1$), ascitic leak ($n = 1$), pneumonia ($n = 3$), vesicle leak ($n = 1$), packed red blood cells (PRBCs) transfusion ($n = 3$), fresh frozen plasma (FFP) transfusion ($n = 1$) and platelets transfusion ($n = 1$); two grade 3 complications (morbidity 13.3 %), which included eventration and soft tissue collection. One patient died suddenly on the 11th postoperative day (mortality 6.6 %) while she was recovering from respiratory complications. Thirteen out of 15 were discharged home by postoperative day 28, and 14 out of 15 by day 90 (one patient deceased).

Discussion

Our patient population age was older than other reported series but the co-morbidities prevalence was standard [12]. Our total IV fluid infusion rate of 10 mL kg^{-1} h^{-1} was above the standard requirement for major abdominal surgery (6–8 mL kg^{-1} h^{-1}), but it was not as high as the usual rate described for cytoreductive surgery (12 mL kg^{-1} h^{-1}) [13].

Our group has studied the intra-abdominal fluid flow pattern in an experimental closed-circuit model in piglets [Sánchez García S, Villarejo Campos P, Padilla Valverde D et al. Experimental intraabdominal chemotherapy closed-circuit model with CO$_2$ recirculation. 29th Congreso Nacional de Cirugía, Madrid, November 15th 2012 (abstract), Spanish]. The fluid infused contained methylene blue. The peritoneal cavity was examined afterwards and a consistent pattern staining certain areas of the surface and preserving others was noticed. This problem has been pointed out before [14]. We concluded that such systems did not guarantee a homogeneous distribution of the chemotherapeutic agent across the peritoneal surfaces. Such circumstance could be important not only as far as tumor cell killing capacity, which is out of the scope of the present article, but could also potentially influence early

Table 2 Intraoperative events

Colloid n (%), ml		15 (100)			977 ± 425
Crystalloid n (%), ml		15 (100)			3,836 ± 87
Packed red blood cells n (%), units		9 (60)			4.5 ± 2.6
Platelets pool n (%), units		2 (13.3)			1 ± 0
Fresh frozen plasma n (%), units		2 (13.3)			2.5 ± 0.7
	preHIPEC	endHIPEC	$p*$	End surgery	$p**$
Esophageal temperature (°C)	34.6 ± 1.1	37.4 ± 0.5	0.001	35.9 ± 1.1	0.001
Blood temperature (°C)	34.7 ± 1.0	37.7 ± 0.6	0.001	34.2 ± 0.9	0.001
Cardiac index (L min^{-1} m^{-2})	3.4 ± 0.7	2.8 ± 0.5	0.03	3.2 ± 0.8	0.21
Stroke volume variation (%)	11.8 ± 3.4	14.6 ± 3.6	0.01	14.5 ± 5.2	0.61
Global end-diastolic volume index (mL m^{-2})	645 ± 128	647 ± 104	0.21	679 ± 80	0.55
Extravascular lung water index (mL kg^{-1})	9.3 ± 2.3	8.7 ± 1.9	0.02	11.6 ± 2.9	0.02
Pulmonary vascular permeability index	2.04 ± 0.27	1.94 ± 0.2	0.28	2.30 ± 0.29	0.5
Cardiac performance index (1 min^{-2})	4.25 ± 1.25	4.25 ± 0.9	0.55	5.75 ± 1.7	0.01
SVRI (dyn s^{-1} cm^{-5} m^{-2})	2,188 ± 757	2,040 ± 559	0.55	1,733 ± 273	0.05
Heart rate (bpm)	71 ± 15	88 ± 19	0.01	80 ± 4	0.07
Hemoglobin (g dL^{-1})	9.5 ± 1.4	9.9 ± 2.0	0.64	9.7 ± 2.0	0.87
Prothrombin activity (%)	76 ± 17	76 ± 12	0.64	76 ± 12	0.55
pH	7.35 ± 0.05	7.29 ± 0.05	0.01	7.26 ± 0.06	0.001
PaCO$_2$ (mm Hg)	36 ± 10	35 ± 11	0.14	35 ± 5	0.46
PaO$_2$ (mm Hg)	198 ± 69	171 ± 67	0.02	196 ± 81	0.55
Bicarbonate (mEq L^{-1})	20.8 ± 2.8	17.8 ± 2.6	0.001	19.8 ± 3.5	0.01
Base excess (mEq L^{-1})	−3.8 ± 2.9	−7.6 ± 3.5	0.001	−3.8 ± 5.5	0.001
Lactic acid (mg dL^{-1})	15.3 ± 10.4	32.1 ± 13.4	0.001	24.1 ± 14.7	0.02
Oxygen delivery (mL min^{-1} m^{-2})	415 ± 91	405 ± 92	0.04	419 ± 123	0.65

SVRI Systemic vascular resistance index

* Pre-endHIPEC difference

** EndHIPEC-endSurgery difference

Fig. 3 Timing: *1* preHIPEC; *2* posHIPEC; *3* end surgery; *4* ICU admission; *5* 12 h in ICU. Temperature °C; ELWI mL kg^{-1}; lactate mEq dL^{-1}; heart rate beats per minute
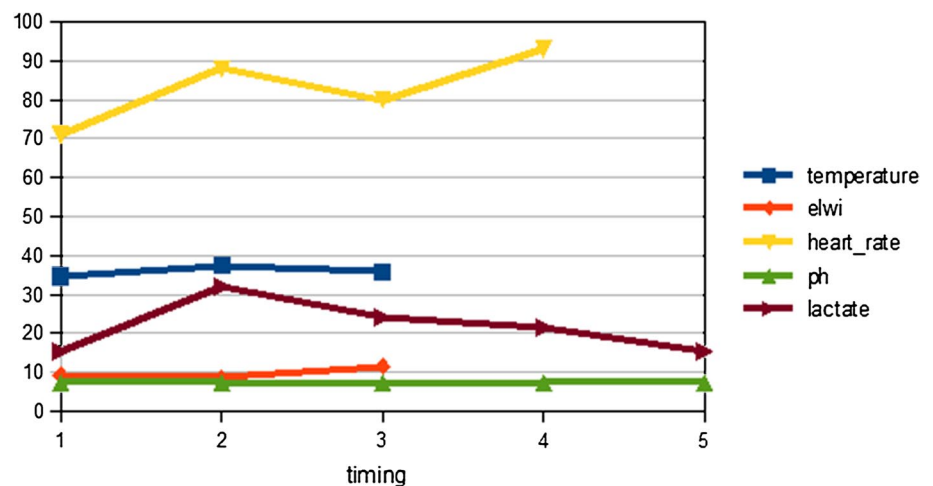
outcomes. This closed system did not induce a temperature raise higher than previously described by the end of the HIPEC phase (top average 37.7 °C) [15]. Heart rate and SVV increased during the HIPEC phase revealing the vasodilatation and relative volume deficit associated with the heat increase [16]. It was not accompanied by a decrease in preload (GEDVI) probably due to the rise of intra-abdominal pressure, a mechanism already described

[17]. CPI was rocky stable, but the resulting CI was slightly decreased. SVRI had a non-significant tendency to decrease. Therefore, we did not encounter the hyperdynamic situation generally described [18], but we have not been the only ones to find this moderate behavior [19]. There was an ELWI elevation before, during and after the HIPEC phase. The possible relation of these data to the low plasma protein content [20] once the ascites is drained has been pointed out [21]. In our case, the preoperative total protein was within a normal range, but it dropped down during the procedure (2.7 g dL^{-1} drop; $p = 0.03$). The low oncotic pressure did not create a lung permeability problem, as PVPI was always preserved normal. The metabolic end-organ demand that parallels temperature was responsible for the moderate lactic acidosis encountered.

Table 3 Admission at ICU

	Mean	SD
Heart rate (bpm)	93	12
Stystolic arterial pressure (mm Hg)	114	21
Respiratory rate (rpm)	16	2
PaFi	386	130
APACHE II*	12	(10–13)
Predicted mortality (%)	16.2	10.0
SAPS*	42	(37–47)
Hours to extubation	11.6	17.4
1st day highest blood temperature (°C)	37.0	3.7
1st day lowest temperature (°C)	35.2	0.9

* Median 25–75th ‰

There has been some debate about the risk–benefit of using a perioperative LTE [22]. We, as others [23], did not detect a difference in hemodynamic parameters or IVF management during the procedure (total amount of IV fluid $p = 0.6$; GEDVI $p = 0.4$; SVV $p = 0.9$) associated with the presence or not of an LTE. There were two cases with a postoperative platelet count below 100,000 but above 50,000, which should not represent a problem at the time of removing the catheter. We conclude that LTE can be safely but judiciously used for perioperative management.

Renal function was well preserved without difficulty, just as already known [24]. No hyperglycemia, hyponatremia [25] or hyperkalemia was noted in our series. Laboratory analysis revealed a moderate intraoperative change in coagulation parameters: decrease of prothrombin activity (PT) to 76 %, no change in activated partial thromboplastin time and a reduced number of thrombocytes compared to preoperative level, but still within normal limits. These are minor changes compared to findings communicated by other series [26].

The SOFA score was already low on admission at the ICU, and most laboratory values were within normal range except, lactic acid, glucose and hemoglobin, which were close to normal and basically acceptable as postoperative values. Twelve hours latter median SOFA was 0.

Table 5 summarizes early outcomes reported in previous series. Despite the fact that most authors use similar classification systems, there are obvious disparities about the particular criteria applied. Inter-studies variation is enormous and comparisons are problematic at the least. Therefore, conclusions about the effectiveness of our turbulent-flow

Table 4 Perioperative changes

	Preoperative ($n = 15$)	ICU ($n = 15$)	p*	12 h ($n = 15$)	p**
SOFA		3 (2–4)		0 (0–1)	0.001
Hemoglobin (g dL^{-1})	12.2 ± 1.7	9.7 ± 2.0	0.01	10.4 ± 1.6	0.58
Platelets (1,000 μL^{-1})	308 ± 94	188 ± 78	0.001	186 ± 68	0.64
Prothrombin activity (%)	96 ± 8	76 ± 12	0.001	72 ± 11	0.25
aPTT (scs)	29.0 ± 4.0	28.3 ± 6.4	0.58	27.3 ± 3.6	0.75
Fibrinogen (mg dL^{-1})	473 ± 110	263 ± 84	0.001	397 ± 131	0.001
Creatinine (mg dL^{-1})	0.8 ± 0.3	0.8 ± 0.2	0.79	0.9 ± 0.4	0.83
Glucose (mg dL^{-1})	123 ± 31	220 ± 55	0.001	179 ± 47	0.03
Bilirubin (mg dL^{-1})	0.47 ± 0.17	1.05 ± 0.7	0.02	0.68 ± 0.3	0.4
Total protein (g dL^{-1})	6.4 ± 1.4	3.7 ± 1.1	0.03	3.5 ± 0.5	0.59
Sodium (mmol L^{-1})	139 ± 2	140 ± 3	0.5	141 ± 4	0.09
Potassium (mmol L^{-1})	4.5 ± 0.3	3.6 ± 0.4	0.001	3.7 ± 0.4	0.59
pH		7.38 ± 0.06		7.37 ± 0.06	0.48
pCO$_2$ (mm Hg)		35 ± 5		38 ± 6	0.09
pO$_2$ (mm Hg)		191 ± 98		122 ± 31	0.01
Bicarbonate (mmol L^{-1})		20.9 ± 3.5		22.1 ± 4.2	0.42
Base excess		−3.4 ± 4.3		−3.1 ± 4.3	0.55
Lactic acid (mg dL^{-1})		21.5 ± 12.5		15.3 ± 10.4	0.03

Data presented as: median (25–75th ‰); otherwise presented as mean ± SD

aPTT activated partial thromboplastin time

* Preoperative to ICU admission difference

** Admission to 12 h difference

Table 5 Previous series reporting early outcomes and complications on hyperthermic peritoneal chemotherapy for ovarian cancer

	Ref.	N	Inclusion	Temperature (°C)	Time minutes	Agent	Surgery hours	LOS days	Mortality (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Present series		15	A/R	41–43	60	Paclitaxel	8	12.7	6.6	80	46.7	13.3	6.6
Argenta et al.	[27]	10	R	40–43	90	Carboplatin	NR	5.5	0	60		20	
Frenel et al.	[28]	31	A/R	41.5–42.5	30	Oxaliplatin	6	11	0	3.3	3.3	29	3.3
Ansaloni et al.	[29]	39	A/R	41.5	60–90	Doxorubicin cisplatin paclitaxel		23.8	2.5	18		8	
Tentes et al.	[30]	43	A/R	42.5–43	90	Cisplatin doxorubicin gemcitabine	NR	NR	5	48.8	35.2	9.3	4.7
Königsrainer et al.	[31]	31	R	42	90	Cisplatin	10	14–18	0	3	7	48	13
Fagotti et al.	[32]	41	R	41.5	30	Oxaplatinum	5.5	NR	0	NR		49	
Cascales Campos et al.	[33]	46	A/R	42–43	60	Paclitaxel	7.3	7	0	22		15	
Deraco et al.	[34]	26	A	42.5	90	Cisplatin doxorubicin	10.3	21	4	16		20	
Roviello et al.	[35]	53	A/R	41–43	60	Cisplatin mitomycin c	8	10	0	42		23	
Pomel et al.	[36]	31	A	42–44	30	Oxaliplatin	NR	NR	NR	NR		29	
Celeen et al.	[37]	42	R	40.5–41	30–90	Cisplatin oxaliplatin	8.3	16	0	43		21	
Lim et al.	[38]	30	A	41.5	90	Cisplatin	9.5	17	0	73	90	40	0
Bereder et al.	[39]	246	A/R	42	90	Cisplatin doxorubicin mitomycin c	N	17	0.4	NR	NR	12	NR
Pavlov et al.	[40]	56	A/R	40	120	Doxorubicin cisplatin	5	14	2	5	11	0	2
Guardiola et al.	[41]	47	A	37	120	Cisplatin	7.2	18	0	NR	NR	NR	13
Di Giorgio et al.	[42]	47	A/R	42–43	60	Cisplatin	9	22	4	NR	21	9	13
Bae et al.	[43]	67	A	43–44	90	Carboplatin paclitaxel	N	N	0	14	13	0	0
Cotte et al.	[44]	81	R	44–46	90	Cisplatin	4	17	3	6	1	5	2
Helm et al.	[45]	18	R	41–43	90	Mitomycin cisplatin	10	12	6	11	50	40	13
Rufián et al.	[46]	33	A/R	41–43	60	Paclitaxel	5	11	0	12	10	10	6
Raspagliesi et al.	[47]	40	R	42.5	NR	Mitomycin c doxorubicin cisplatin	7	21	0	20	NR	NR	NR
Look et al.	[48]	28	A	NR	90	Cisplatin and doxorubicin mitomycin c 5FU	NR	NR	0	NR	NR	7	4
Ryu et al.	[49]	57	A	43–44	90	Carboplatin interferon	NR	NR	4	14	50	NR	4
Piso et al.	[50]	19	A/R	NR	90	Cisplatin mitoxantrone	9	25	5	10	10	10	15
Zanon et al.	[51]	30	R	41.5	60	Cisplatin	6	12	3	27	3	7	7
Chatzigeorgiou et al.	[52]	20	R	39–40	120	Cisplatin	NR	12	10	70	20	0	0
de Bree et al.	[53]	19	R	41	NR	Docetaxel	NR	NR	10	10	20	0	10

R recurrent, *LOS* length of stay in hospital; some studies distinguish only between minor (grades 1 and 2) and major complications (grades 2 and 3), *A* advanced

device cannot be based on direct comparison between different systems. Our immediate postoperative outcome was reassuring per se. During the initial hours in the ICU, the evolution was very favorable. We did not find some of the problems previously attributed to HIPEC, as hyperdynamic status or coagulopathy.

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