Which method to deliver hyperthermic intraperitoneal chemotherapy with oxaliplatin? An experimental comparison of open and closed techniques.

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Running title: Experimental comparison of open and closed HIPEC

Synopsis: This experimental pharmacokinetic comparison between open and closed techniques of HIPEC was performed in a swine model using oxaliplatin. Good thermal homogeneity was achieved with both techniques. The systemic absorption and the abdominal tissue uptake of oxaliplatin were higher with the open techniques. The overall operative time in the two techniques was not significantly different.

ABSTRACT

Background. Heated intraperitoneal chemotherapy (HIPEC) achieves good results in selected patients with peritoneal carcinomatosis. There are two main procedures to deliver this therapy: the open abdomen and the closed abdomen technique. A true comparison of the two techniques has never been performed and is lacking in the literature. The aim of this study was to compare blood and abdominal tissue concentrations of oxaliplatin after open and closed techniques to deliver HIPEC.

Methods. Nine pigs underwent a HIPEC at 42-43°C for 30 minutes using oxaliplatin (400 mg/m^2) according to two techniques: closed (3 animals) or open (6 animals). Open technique used either an external heater with a pump (3 animals) or an intra-abdominal heating cable (3 animals) to achieve hyperthermia. Temperature homogeneity, systemic absorption and abdominal tissue mapping of the penetration of oxaliplatin with each technique were studied. Two additional pigs underwent hyperthermia using dyes instead of oxaliplatin to depict the distribution of the liquid within the abdomen with both techniques.

Results. Hyperthermia was satisfactory with both techniques. The closed technique achieved higher temperatures within the diaphragmatic area, while the open obtained higher temperatures in the mid and lower abdomen (p<0.001 for both comparisons). The systemic absorption of oxaliplatin was higher with the open technique (p<0.04 for all comparisons), as was the accumulation within the abdominal cavity. The operating time for the two techniques was not significantly different.

Conclusion. Intraperitoneal hyperthermia can be achieved with both techniques. The open technique showed significantly higher systemic absorption and abdominal tissue penetration of oxaliplatin than the closed technique.

INTRODUCTION

Cytoreductive surgery followed by heated intraoperative peritoneal chemotherapy (HIPEC) is increasingly recognized as the first therapeutic choice in patients with peritoneal malignancies [1, 2]. An overall survival rate as high as 51% can be achieved in selected patients with peritoneal carcinomatosis of colorectal origin submitted to HIPEC [3]. There are now sufficient data to provide strong evidence regarding the interest of this technique and international consensus is being reached [4-6]. However, there is still no uniformity in the technique used to administer HIPEC.

There are mainly two types of HIPEC: one in which the abdomen is left open during chemotherapy (inspired by Sugarbaker's "coliseum" technique) and another in which the abdomen is closed [7]. In open-abdomen HIPEC, the liquid can be stirred permanently to ensure temperature homogeneity, good distribution of the liquid and theoretically optimal delivery of the drugs. Its main disadvantages are heat dissipation and the risk of exposure of the surgical team to the chemotherapy drugs and their potential toxic, teratogenic and mutagenic effects. The closed-abdomen procedure avoids exposure to the chemotherapy drugs but it carries the drawback of uneven distribution of the heated chemotherapy within the abdomen [2, 8]. This is less satisfactory as some peritoneal surfaces may be under treated whereas others may suffer thermal injuries [9]. Our group described a way to combine the two techniques: it consists in performing HIPEC while keeping the abdomen open but isolated in a sort of "glove box". This technique is a true open technique but avoids exposing the personnel to the chemotherapy drugs and could reduce the heat dissipation which occurs with the "coliseum" technique [10, 11]. With this combined technique, hyperthermia can be achieved either by a classical heating pump or by a heating cable, as it has been shown elsewhere [12]. As stated by the International Peritoneal Surface Oncology Group after the 2006 meeting in Milan, the debate on the best method to deliver HIPEC is still open and there is insufficient

evidence in the literature to confirm the superiority of one technique. Each institution

becomes familiar with one machine and learns to troubleshoot that particular device. This

enables each institution to standardize the delivery of HIPEC [2]. However, a global

comparison of the techniques of HIPEC, with homogeneous methods and within the same

research program, has never been performed. Thirty minutes of HIPEC with oxaliplatin is an

increasingly used therapeutic regime, particularly for peritoneal carcinomatosis of colorectal

origin [3, 13, 14]. This regime was chosen for the present comparison. The aim of this study

was to perform an experimental comparison between open and closed HIPEC in terms of

thermal homogeneity, systemic absorption and tissue delivery of oxaliplatin.

ANIMALS AND METHODS

Animals. Eleven 3-month-old large white female pigs weighing 50-60 kg were used. All of the pigs were allowed to acclimatize to the laboratory environment for 7 days with free access to standard food and water. They were then operated on and killed at the end of the procedure with an intravenous injection of pentobarbital (Dolethal®, Vétoquinol, France). This project was approved by the Animal Ethics Committee of the University of Burgundy, France, and conducted upon the Helsinki recommendations.

Anesthesia. Anesthesia was induced by intramuscular injection of 5-10 mg/kg ketamine + 1 mg atropine, and then completed by intravenous ketamine and sufentanil until endotracheal intubation. The animals were maintained under anaesthesia by isoflurane (minimum alveolar concentration = 1), intravenous sufentanil and cisatracurium. Heart rate, electrocardiogram, esophageal temperature and oxygen blood saturation were measured using the NICO system (Novametrix Medical Systems Inc., Wallingford, CT). Fluid resuscitation was achieved with isotonic saline and Ringer lactate with a mean volume of 2 litres per pig.

Surgical technique. A large midline laparotomy was performed to access the abdomen. HIPEC was then performed according to the following schedule:

- <u>Animals 1 and 2</u> underwent 30 minutes of intraperitoneal hyperthermia at 42-43°C with a mix of two dyes (10 ml of Bleu Patente, Guerbet, France + 5 ml Indigo Carmin 0.8%, Serb SAS, France), in 4 litres of previously heated 50 g/l glucose (Baxter, UK). The closed technique was used on the first animal, with two inflow tubes (30F, Bard, Boston, USA) under each hemi-diaphragm and one outflow 32 Fr catheter in the Douglas space. In the second animal, an open technique was performed using a covered abdominal cavity expander, with constant stirring of the liquid and sequential opening of the peritoneal spaces [10]. Three temperature probes (Tyco, USA) were placed inside the abdomen (one fixed with a stitch to the diaphragm, one in the

mesentery and the last into the Douglas space), and two other probes were positioned inside the inflow and the outflow tubes. HIPEC was performed in both animals using a closed continuous circuit (Dideco, Italy), a roller pump (Cobe, Stöckert, Germany), a heat exchanger (Dideco, Italy) and an integrated system of real-time temperature control and monitoring (Bodytherm 8180, version 1.2.0, EFS électronique, France). A continuous recording was obtained for the flux and the temperature in each thermal probe. At the end of each procedure, the animals were killed and a comprehensive abdominal examination was performed to assess the distribution of the blue dye.

- <u>Animals 3 to 11</u> underwent 30 minutes of HIPEC with oxaliplatin (400 mg/m^2), at 42-43°C, in 4 litres of glucose 5% which had previously been heated to 43°C. The total dose of drug per animal was 600 mg. The oxaliplatin was added to the liquid when the minimal target temperature (42°C) was obtained in all the abdominal temperature probes. *Animals 3 to 5* had closed HIPEC with the previously described heating pump (HP). A pressure probe (a Palmer needle connected to a water column) was placed at the level of the mesenteric root in all closed techniques and the pressure measured every 5 minutes. A 14G catheter was inserted through the abdominal wall close to the midline to drain the air retained within the abdomen during the closure of the laparotomy. *Animals 6 to 8* underwent open HIPEC using the covered abdominal cavity expander and the heating pump. As before, temperature probes were placed inside the abdomen (one fixed with a stitch to the diaphragm, one in the mesentery and the last into the Douglas space), and two other probes were positioned inside the inflow and the outflow tubes (Tyco, USA). The flow rate was adjusted to maintain a target temperature of 42 to 43°C. The procedure was conducted in the same way in *animals 9 to 11*, but two 17-metre length insulated electric heating cables (HC) were used to achieve hyperthermia instead of the classical external circuit, as described by

our group [12]. One HC was distributed in the supramesocolic area and the other in the inframesocolic area and between the bowel loops. They were switched on or off to obtain the targeted temperatures in both regions. In the open procedures, the surgeon used his hand to constantly stir the liquid and sequentially open the different abdominal spaces.

At the end of the procedure, the liquid was sucked out and tissue sampling was performed. The time to set up the different HIPEC systems, to reach the target temperature before HIPEC, and to dismantle the system were recorded as was the overall operative time. All of the viscera were then carefully examined to look for thermal injury. Any lesion or doubtful area was removed and sent to the pathologist for histological examination. The fluid containing chemotherapy was destroyed in accordance with French regulations for the disposal of chemotherapy drugs.

Blood, circuit and tissue sampling. Seven blood samples were collected for each animal at different times: at time 0 (when the temperature reached at least 42°C in all thermal probes), and every 10 minutes during the 30-minute HIPEC procedure. Blood samples were also collected after the end of the HIPEC procedure, at 40, 50 and 60 minutes from time 0.

Five samples of peritoneal fluid were collected for each animal at different time points: at time 0 when the peritoneal fluid reached 42°C in all thermal probes, and at 5, 10, 20 and 30 minutes during HIPEC.

At the end of the procedure, 15 peritoneal samples (size: 5 x 5 mm) were harvested at the following sites, inspired by Sugarbaker's Peritoneal Carcinomatosis Index [15]: parietal peritoneum close to the incision, left diaphragm, right diaphragm, posterior aspect of the stomach, left paracolic gutter, right paracolic gutter, right pelvic parietal peritoneum, left pelvic parietal peritoneum, ovary, proximal jejunum, distal jejunum, proximal ileum, distal

ileum, colon and mesentery. Samples of bowel always comprised a full-depth fragment. All samples were immediately frozen at -20°C until platinum assay.

Platinum assay. The tissues or an aliquot of 1 ml of whole blood were weighed and digested with 5 ml HNO_3 65 % + 1 ml H_2O_2 in a microwave oven. The mineralisat was poured into a 10 ml tube and the volume completed to 10 ml with ultra pure water. The platinum concentration was measured with a high-resolution continuum source atomic absorption spectrometer (ContrAA 700, AnalytikJena, Germany). The results were corrected according to the dilution and the sample weight and a concentration in mg/kg was obtained. Platinum is about half of the molecular mass of oxaliplatin; to convert platinum concentrations into oxaliplatin concentrations, the first must be multiplied by 2.03.

Statistical analysis. Concentrations of platinum (mg/kg), temperature (°C) and time (minutes) are presented as means ± standard deviation in the text and tables. Median values are presented in the figures as specified, but were not used for the statistical analysis. Only the nine animals undergoing true HIPEC (animals 3 to 11) were considered for the pharmacokinetic analysis. All animals were included for the temperature analysis. Because of the small sample size, non-parametric tests were used to analyse the concentrations of platinum and the operative time. A Kruskal-Wallis test was performed for the comparison of more than two means and if different, the Mann-Whitney's test was used for 2 x 2 comparisons between groups. Prior to considering a pooled analysis of animals 6 to 8 (open HIPEC with the heating pump) and animals 9 to 11 (open HIPEC with the heating cable), the absence of any difference between the two groups was assessed with a Wilcoxon test. A Levene test was performed to assess the heterogeneity of variances between the groups. Decimals were always conserved for calculation, but only 2 decimals are shown for platinum concentration. The continuous temperature recording in each thermal probe was transformed into a discontinuous variable using the temperature recorded every 2 seconds. Parametric tests

were used for the temperature analysis (Student's t test or ANOVA, as appropriate). A two-tailed p of < 0.05 was considered significant for all tests. Data collection and statistical calculations were performed using SPSS (version 10.0) software.

RESULTS

All procedures ran uneventfully and no intraoperative complications were observed. There was no thermal injury in any case. Mean operative times were 104 ± 13 minutes, 132 ± 21 minutes and 110 ± 16 minutes, in the closed technique, the open HP technique and the open HC technique, respectively (no significant difference). The intra-abdominal mesenteric pressure ranged between 14 and 20 cm H_2O in the four closed procedures.

Staining experiences. The *first animal* was subjected to closed hyperthermia at 42-43°C for 30 minutes. Staining of the diaphragm, the urinary bladder and the Douglas space was observed. The colouring was less marked on the gallbladder, the liver, the anterior aspect of the stomach and the colon. It was heterogeneous on the small bowel (with coloured and non coloured segments) and there was no colouring at all on the posterior aspect of the stomach, the pre-rrenal peritoneum (on the right as on the left) and in the parietal peritoneum around the midline. The *second animal* showed more intense staining of the diaphragm, the parietal peritoneum, the gallbladder, the urinary bladder, the Douglas space and the colon after 30 minutes of open hyperthermia. The colouring was evident but less marked on the small bowel, the liver and the stomach.

Platinum analysis. There was no difference between the HIPEC techniques with regard to platinum concentrations within the *intra abdominal liquid*. Half of the oxaliplatin dose was absorbed in 30 minutes with all three techniques (the concentrations at that time were 41.9 ± 14.5; 42.55 ± 10.12 and 43.78 ± 9.32, for the closed, open HP and open HC techniques, respectively; $P = 0.7$, Kruskal-Wallis test). The concentrations of platinum in *peripheral blood* during HIPEC and in the 30 minutes following the procedure were significantly higher for the open techniques at every time (figure 1). They were also higher for the HC than for the HP system of open HIPEC. Prior to considering animals 6 to 8 (open HP technique) and 9 to 11 (open HC technique) together as a sole group for further statistical analysis of tissues (open

HIPEC), we checked that the concentrations at every time and in every abdominal tissue sample were not different between both groups (p > 0.1 for all comparisons in the Kruskal-Wallis test).

The median tissue concentrations of platinum obtained with each technique are shown in figures 2 and 3. Parietal and visceral peritoneal surfaces are presented separately. The tissue concentrations of platinum were significantly or almost significantly higher for the open techniques in most sites (tables 1 and 2). When the tissue concentrations achieved with all three methods (closed, open HP and open HS) were compared as independent groups, the differences were significant in 2 of the 15 sampled sites (left paracolic gutter and distal ileum, P = 0.04) and was close to significance in 6 other sites (incision, right pelvic peritoneum, ovary, colon, proximal ileum and distal jejunum; P = 0.05, 0.05, 0.06, 0.06, 0.07 and 0.08, respectively).

Temperature analysis. Hyperthermia (between 42°C and 43°C) was obtained and easily maintained with all three methods. The mean temperatures achieved with each technique are presented in table 3. The closed technique achieved a higher temperature than the open techniques in the diaphragm probe, but a lower one in the mesentery and pelvis probes. The flow rate used in the closed technique ranged between 0.5 and 1.5 l/min, while the open technique with the heating pump required higher flows to maintain hyperthermia (between 1.3 and 2.2 l/min). The inflow temperature was never higher than 45.5°C in any case. The time to reach 42°C in the three abdominal thermal probes was significantly longer with the closed technique (31.7 ± 20.2 minutes) as compared with both open techniques (13.7 ± 2.3 minutes for HP and 8.7 ± 3.2 minutes for HC; P = 0.03).

Operative time. The total time to set up and dismantle was longer with the open techniques (36 ± 5 minutes; no difference between HP and HC) than with the closed one (23 ± 6 minutes; p = 0.037 for the Wilcoxon test). These differences did not have an impact on the overall

operative time, which was not different between the two techniques. After a comprehensive examination of all abdominal viscera at the end of the procedure, no thermal injury was detected in any case.

DISCUSSION

Nowadays, the way to deliver HIPEC is a matter of choice for each team according to preferences which are not always based on scientific evidence, but on acquired habits or on fears of exposing the personnel to chemotherapy drugs with the open techniques. In theory, open techniques may have less associated morbidity and better efficacy because of improved heat and drug distribution; however, they also carry a higher risk of exposure of the personnel to the adverse effects of chemotherapy drugs and increase heat dissipation. All these "theories" remain to be proven prospectively and there is no consensus on this topic [2, 8].

The search for ways to distribute chemotherapy drugs homogeneously within the abdomen has been present since the beginning of intraperitoneal chemotherapy [16]. Elias et al performed a phase I-II trial in which they successively tested seven HIPEC procedures [10]. The comparison was made in terms of technical feasibility, thermal homogeneity and methylene blue distribution (only in the last patients) within the abdominal cavity; the authors concluded that the open technique with traction of the skin upwards was superior. The hypothesis of preferential circuits with the use of closed techniques was then raised.

Our study is the first to compare open and closed HIPEC techniques in terms of thermal homogeneity and diffusion of the chemotherapy drug, measured both in the peripheral blood and with mapping of uptake in abdominal tissues.

Hyperthermia was effectively achieved with both the open and closed techniques, but the closed technique achieved a higher temperature in the diaphragmatic regions, while the open technique was more effective in the other areas. This is certainly due to the proximity of the inflow tubes to the diaphragm in the absence of stirring in the closed techniques. Higher heat dissipation in the open technique may explain the need for a higher flow rate when the heating pump was used. However, an inflow temperature higher than 45.5°C was never required, and the risk of thermal injuries was therefore low with both techniques. As

previously described, the heating cable was a simple and safe way to achieve homogeneous hyperthermia [13]. This method showed to be at least as effective as the classical circuits and devices for open HIPEC. Despite achieving higher concentrations in the tissues than with the "classical" heating device with a closed circuit (open HP), the difference did not reach statistical significance at any site of the abdominal cavity map. However, systemic absorption was significantly higher with the heating cable.

Gesson-Paute et al. recently published an experimental study comparing the pharmacokinetics of oxaliplatin with heated intraoperative intraperitoneal oxaliplatin performed by laparotomy versus hand-assisted laparoscopy in a swine model [17]. Indeed, they compared two open techniques of HIPEC (laparotomy vs. hand-assisted laparoscopy with permanent manipulation of viscera and manual adjustment of the inflow drain), and not an open and a closed technique as they claimed. Hyperthermia was successfully achieved with both techniques, although the targeted temperature was obtained faster with the laparoscopic method. There was a faster tissue absorption of oxaliplatin in the laparoscopic group (probably related to the higher pressure during the laparoscopy but no data were given regarding the pharmacokinetics of oxaliplatin according to the intra-abdominal pressure). Later on, the authors provided the results of the tissue oxaliplatin concentration (in the liver, peritoneum and omentum), which were significantly higher in the laparoscopy group [18], but they did not map uptake in the peritoneal cavity during their procedures to assess the homogeneity of the oxaliplatin distribution. These results seem to confirm the enhanced penetration of chemotherapy drugs with high intra-abdominal pressure, which had been shown by our group in a rat model of peritoneal carcinomatosis, both in peritoneal tumours and healthy peritoneum [19]. However, the beneficial effect of high intra-abdominal pressure that could be theoretically obtained with the closed techniques may be counterbalanced by the presence of preferential circuits with areas of the abdominal cavity undertreated during

HIPEC. As a matter of fact, a prospective comparison of open and closed techniques of HIPEC in terms of survival, morbidity or pharmacokinetics is really lacking in the literature [20].

Some authors could argue that a classical open "coliseum technique" (as originally described by Sugarbaker) should have been chosen for the present comparison. Our method of open HIPEC (the so-called "semi-open HIPEC") is in fact a true open technique; the abdomen is kept open and the surgeon's hand can stir and distribute the liquid within the abdomen throughout the procedure without the risk of spillage that persists with the "coliseum" technique [8, 11, 21]. Adding a transparent cover may decrease heat dissipation, which explains why the target temperature was reached quickly (time close to that obtained with hand-assisted laparoscopy [17]), but it does not reduce the efficacy of the distribution of heat and drugs within the abdomen; the cover in no way transforms an open technique into a closed one from the pharmacokinetic point of view.

In the present study, half of the initial oxaliplatin dose was absorbed in 30 minutes of open HIPEC, which is concordant with other authors [14, 22]. The systemic absorption was significantly higher with the open techniques than with the closed technique (and higher with the HC than with the HP). Our results suggest that the open technique is superior in terms of abdominal distribution of oxaliplatin in most abdominal regions, which was associated with a higher peripheral blood concentration. We also found that the concentrations in the parietal surfaces were higher than those in the visceral surfaces. This is certainly due to the choice of total depth sampling in the bowel, which "diluted" the platinum when the measure was corrected using sample weights.

One limit of this study is the absence of previous cytoreductive surgery which could modify oxaliplatin absorption. This is due to the absence of an animal model of peritoneal carcinomatosis close to that in humans. Our results show that better distribution of

chemotherapy drugs is achieved with open techniques. Even though chemotherapy uptake is probably increased by the previous cytoreductive surgery and the possible presence of residual macro or microscopic disease, the exposure of some areas is certainly lower with the closed technique, resulting in lower uptake. The amount of absorbed drug could change, but not the distribution. Moreover, it has been shown that intratumoral drug penetration was similar to absorption at the normal peritoneal surface [14, 19]. Thus, we think that these experiments accurately depict what will happen after complete cytoreductive surgery and in the presence of residual disease.

As previously commented, the mean temperatures obtained in the upper abdomen were significantly higher with the closed techniques, while in the mid and lower abdomen they were higher with the open techniques. An additional interesting feature was that this thermal asymmetry was coupled with asymmetry in tissue uptake. Within the closed technique, higher concentrations of oxaliplatin were obtained in the upper abdominal regions (particularly in the right and left diaphragm) than in the lower abdomen. This could be explained by the well-known enhanced penetration of chemotherapy in the presence of hyperthermia, and confirms that good thermal homogeneity is necessary to achieve good tissue uptake. The heating cable seemed to achieve higher concentrations in these areas as compared with the classical heating device (figures 2 and 3), but the difference did not reach statistical significance.

We can conclude that hyperthermia can be safely achieved with both, open and closed techniques. Open techniques showed significantly higher systemic absorption of oxaliplatin. They also showed significantly higher accumulation of oxaliplatin within most abdominal regions except for the diaphragmatic area. These data suggest that the thermal profile and the penetration of oxaliplatin into tissues are related. Using a heating cable within the abdomen to achieve hyperthermia is at least as effective as a closed circuit with a heating pump.

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Table 1. Mean values of platinum in the peritoneum (mg/kg) in closed and open techniques (mean ± SD).

	Closed	Open	*p* value*
Close to midline	5.10 ± 1.53	38.82 ± 24.31	0.01
Left diaphragm	47.24 ± 6.34	37.50 ± 16.99	NS
Right diaphragm	41.98 ± 3.37	39.40 ± 23.33	NS
Left paracolic gutter	31.37 ± 3.15	61.12 ± 21.52	0.01
Right paracolic gutter	27.73 ± 18.88	52.57 ± 18.61	0.05
Right pelvic peritoneum	19.89 ± 4.49	56.53 ± 29.44	0.01
Left pelvic peritoneum	23.94 ± 9.74	59.37 ± 22.13	0.06

*Mann-Whitney test. NS: not significant.

Table 2. Mean values of platinum in the abdominal visceral peritoneum (mg/kg) in closed and open techniques (mean ± standard deviation).

	Closed	Open	*p* value*
Stomach	7.62 ± 5.15	7.40 ± 2.32	NS
Ovary	0.98 ± 0.14	4.71 ± 2.01	0.01
Proximal jejunum	4.10 ± 3.01	6.68 ± 2.88	NS
Distal jejunum	3.70 ± 1.52	7.37 ± 3.05	0.02
Proximal ileum	2.69 ± 1.69	7.29 ± 1.92	0.01
Distal ileum	1.59 ± 0.64	6.84 ± 2.08	0.01
Colon	2.28 ± 0.45	9.55 ± 3.8	0.01
Mesentery	2.90 ± 2.12	14.32 ± 9.68	0.05

* Mann-Whitney test. NS: not significant.

Table 3. Mean temperature ± standard deviation obtained in each group (°C). The *p* value corresponds to the comparison of the three means with the ANOVA test.

	Closed	**Open HP**	**Open HC**	*p* **value**
Oesophagus	38.2 ± 0.8	38.8 ± 0.4	37.9 ± 2	P < 0.001
Diaphragm	42.7 ± 0.4	42.1 ± 0.7	42.3 ± 0.6	P < 0.001
Mesentery	41.5 ± 0.8	42.2 ± 0.4	42.9 ± 0.4	P < 0.001
Douglas	42.2 ± 0.2	42.6 ± 0.6	42.7 ± 0.4	P < 0.001

Figure 1. Mean peripheral blood concentration of platinum ± standard deviation with each technique of HIPEC. "Open pump" (■) denotes open HIPEC with the open circuit, the heat exchanger and the roller pump. "Open cable" (▲) denotes open HIPEC with the heating cable. "Closed" (♦) denotes the closed HIPEC. The blood concentrations were significantly different at every time: (*) P = 0.027 and (**) P = 0.038, according to the Kruskal-Wallis test. When both techniques of open HIPEC were considered together as a sole group and compared with the closed technique, the Mann-Whitney test yielded a P = 0.01 for each comparison.

Figure 2. Median platinum concentration in the abdominal viscera with each technique of HIPEC. "Open pump" denotes open HIPEC with the open circuit, the heat exchanger and the roller pump. "Open cable" denotes open HIPEC with the heating cable. Gastr: posterior aspect of the stomach; Ovar: ovary; Prox: proximal; Dist: distal; J: jejunum; I: ileum; Mesent: mesentery.

Figure 3. Median platinum concentration in the parietal peritoneum with each technique of HIPEC. "Open pump" denotes open HIPEC with the open circuit, the heat exchanger and the roller pump. "Open cable" denotes open HIPEC with the heating cable. Incis: parietal peritoneum close to the laparotomy; L: left; R: right; Diap: diaphragm; PCG: paracolic gutter; PP: pelvic peritoneum.