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Complications related to hyperthermia during hypertermic intraoperative intraperitoneal chemiotherapy (HIPEC) treatment. Do they exist?

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Abstract. – *Background and Objectives:* **Hyperthermia, either alone or in combination with anticancer drugs, is becoming more and more a clinical reality for the treatment of far advanced gastrointestinal cancers, acting as a cytotoxic agent at a temperature between 40-42.5°C.**

Although hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is demonstrated to have some benefit in selected patients with peritoneal seeding, there are not enough data on the risk of damage of normal tissue that increases as the temperature rises, with possible serious and, sometimes, lethal complications.

Materials and Methods: **We searched on medline words like "intraoperative intraperitoneal chemohyperthermia and morbidity", focusing our attention on studies (published since 1990) which reported morbidity as bowel obstruction, bowel perforation or anastomic leak, during intraoperative intraoperitoneal chemotherapy in hyperthermia (HIPEC).**

Results: **Heat acts increasing cancer cell killing after exposure to ionizing radiation, inhibiting repairing processes of radiation-induced DNA lesions (radiosensitization), and also sensitizing cancer cells to chemotherapeutic drugs, particularly to alkylating agents (chemosensitization). The peritoneal carcinomatosis (a frequent evolution of advanced digestive cancer) represents one of the main indication to hypertermic treatment. In the last fifteen years, in fact, different methods were developed for the surgery treatment (peritonectomy) and for loco-regional chemotherapic treatment of the carcinomatosis (intraperitoneal intra/post-operative iper/normothermic chemotherapy) to act directly on neoplastic seeding. We found, as result of different studies, 9 articles, written about perforation after HIPEC.**

Conclusion: **The aim of the present study is to present the review of the literature in terms of peri-operative complications related to the hyperthermia during intraoperative chemohyperthermia procedure.**

Key Words:

Hyperthermia, HYPEC, Chemotherapy, Complications.

Introduction

Hyperthermia, either alone or in combination with anticancer drugs, is becoming more and more a clinical reality for the treatment of far advanced gastrointestinal cancers, acting as a cytotoxic agent at a temperature between 40-42.5°C[1].

The peritoneal carcinomatosis (a frequent evolution of advanced digestive cancer) represents one of the main indication to hypertermic treatment. Peritoneal seeding is synchronous to the cancer in the 20-30% of cases, and it is the most frequent form of recurrence (15-40%) in those patients with gastric cancer and the second form of recurrence in those patients with colon cancer[2,3].

The carcinomatosis was always considered in the past, and often today, a terminal condition and it was only treated with palliative treatment. In the last fifteen years, thanks to the technological progress and positive results of more aggressive multimodal approaches on the treatment of intestinal recurrences and liver metastases, the approach of the treatment of peritoneal carcinomatosis was radically changed. For a long time, Sugarbaker and others Authors studied, this aspect. In selected cases, they focused their attention on the opportunity, of a complete eradication of the peritoneal disease to obtain better results for a longer term survival[4-6].

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However, although hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is demonstrated to have some benefit in selected patients with peritoneal seeding, there are not enough data on the risk of damage of normal tissue that increases as the temperature rises, with possible serious and, sometimes, lethal complications.

The aim of the present study is to present the review of the literature in terms of peri-operative complications related to the hyperthermia during intraoperative chemohyperthermia procedure.

Background

Hyperthermia Physical and Chemical Effects

Heat acts increasing cancer cell killing after exposure to ionizing radiation, inhibiting repairing processes of radiation-induced DNA lesions (radiosensitization), and also sensitizing cancer cells to chemotherapeutic drugs, particularly to alkylating agents (chemosensitization)[7-16].

Hyperthermia acts as a cytotoxic agent on the cell membrane, especially on the membrane proteins more than on the membrane lipids[17]. In particular, heat causes conformational changes of membrane proteins, followed by instability of the phospholipid bilayer and by an altered permeability to cations through the cell membrane. In fact, an increased K^+ efflux as well as an enhanced Ca^{2+} and H^+ influx have been demonstrated[18-19].

Changes are induced not only on the cell membrane but also on the plasmalemma, in the intracellular membrane structures and on the cytoskeleton, with a disaggregation of microtubules and microfilaments. Hyperthermia also inhibits DNA replication and protein synthesis and it causes changes in the physicochemical equilibrium and alterations of chemical reactions, including metabolic processes like those producing energy, provoking an ATP depletion[7-16].

Furthermore, hyperthermia induces pathophysiological changes like hypoxia, or even anoxia, acidity, and nutrient and energy deprivation[20-21].

The preferential effect of heat on cancer cells is due to the mostly poor blood flow in cancers when compared with the blood flow in normal tissues[22-25].

Besides, the cytotoxic effect of hyperthermia is not only dependent on the temperature but it is also related to the exposure time. Hyperthermia shows a synergism with certain cytotoxic drugs, increasing, at a higher temperatures, cell-membrane permeability and cancer tissue drugs uptake[26].

Material and Methods

We searched on medline words like “intraoperative intraperitoneal chemohyperthermia and morbidity”, focusing our attention on studies (published since 1990) which reported morbidity as bowel obstruction, bowel perforation or anastomic leak, during intraoperative intraoperitoneal chemotherapy in hyperthermia (HIPEC).

We found, as result of different studies, 9 articles, written about perforation after HIPEC (Table I).

In 1990, Fujimura et al[27] applying HIPEC, after cytoreductive surgery, to 31 patients with gastric cancer for 40 to 60 minutes, with 10 litres of saline perfusion, containing Cisplatinum (CDDP) and Mitomycin C (MMC), with the inflow and outflow temperature of 52°C and 42°C, respectively, reported one intestinal leakage of the anastomosis, and one intestinal perforation, without mortality.

In 1995, Yonemura et al[28] applied HIPEC to 79 patients with gastric cancer. In this study, there was a control group, consisting of 81 patients with gastric cancer, who only underwent curative surgery. The perfusion, containing MMC and CDDP, with the inflow and outflow temperature of 43.5°C and 41.5°C, respectively, lasted 60 minutes. They reported four leakages: two in the control group and two in the HIPEC treated group.

In 1996, Yonemura et al[29] applied for 60 minutes HIPEC to 83 patients with gastric cancer and peritoneal dissemination, using a saline solution, containing MMC, Etoposide and CDDP, at the temperature of 42-43°C. A small bowel perforation was reported in 3 patients.

In 1999, Stephens et al[30] analysed data about 183 patients with various abdominal cancers who, after cytoreductive surgery, underwent for

Table I. Published Series of HIPEC.

Source	Patients No	Primary site	Chemotherapeutic agents	Intraabdominal temperature °C	Perfusion time	Morbidity (percentage)
Fujimura et al 1990[27]	31	Gastric cancer	200 mg CDDP/m^2 20 mg MMC/m^2	42-52	40-60	2 (6.5%)
Yonemura et al 1995[28]	79	Gastric cancer	30 mg MMC 300 mg CDDP	41.5-43.5	60	2 (2.5%)
Yonemura et al 1996[29]	83	Gastric cancer	30 mg MMC 300 mg CDDP 150 Etoposide	42-43	60	3 (3.6%)
Stephens et al 1999[30]	183	Various abdominal	12.5 MMC/m^2 male 10.5 MMC/m^2 female cancer	42-43	90	15 (8.2%)
Yonemura et al 1999[31]	66	Gastric cancer	30 mg MMC 300 CDDP 150 Etoposide	42-43	60	2 (3%)
Shido et al 2000[32]	9	Gastric cancer	150-300 mg CDDP 30-60 mg MMC	42	60	0 (0%)
Samel et al 2000[33]	9	Gastric cancer	15 mg/m^2 MMC 150 mg/m^2 CDDP	43.5	60	1 (11%)
Rey et al 2000[34]	35	Various abdominal cancer	10 mg/L MMC 12 mg/L Cisplatinumum	42	60	3 (8.6%)
Elias et al 2001[35]	64	Colorectal adenocarcinomas	20 mg/m^2 MMC 200 mg/m^2 CDDP	41-44	60	5 (7.8%)

90 minutes HIPEC, using a perfusion containing MMC, at the temperature between 42°C and 43°C. They reported 9 fistula and 6 anastomotic leak.

In 1999, Yonemura et al[31] reported the results of a ten-year period about 106 patients with peritoneal dissemination from gastric cancer. In the group of patients, who underwent the HIPEC, with a saline solution containing MMC, Etposide and CDDP for one hour, at the temperature of 42-43°C, one anastomic leakage and one small bowel fistula were reported.

In 2000, Shido et al[32] investigated the mechanism of the peritoneal damage induced by continuos hyperthermic peritoneal MMC perfusion, and the protein and fluid loss during and after HIPEC, and continuous normothermic peritoneal perfusion (CNPP). They reported no perforations in the two groups of patients that underwent HIPEC (at 42°C for 60 minutes) and CNPP, respectively.

In 2000, Samel et al[33] reported one dehiscent colocolic anastomosis in a group of 9 patients with far advanced gastric cancer, treated with cytoreductive surgery and HIPEC (at 43.5°C for 60 minutes), consisting of a saline solution, containing MMC and CDDP.

In 2000, Rey et al[34] reported three digestive fistulas in a group of 35 patients with various abdominal cancers, treated with cytoreductive surgery and HIPEC (at 43°C for 60 minutes) consisting of a solution containing MMC and CDDP.

In 2001, Elias et al[35] analysing 64 patients with peritoneal carcinomatosis arised from colorectal adenocarcinomas, reported 5 fistula only in those patients who had a HIPEC treatment (at 41-44°C for 60 minutes), with a solution containing CDDP and MMC.

Discussion

We found that the most frequent complication, encountered by the Authors who used HIPEC in their works, are bone marrow suppression, renal failure and anastomotic leakage or perforation. We think that the explanation of complications, like bone marrow suppression or renal failure, are exhaustive, but there is not any explanation about perforation as, for example, we read in a study done in 1990, according to which Fujimura et al[27], who treated a total of 31 patients with

surgery and HIPEC, maintaining the intraperitoneal temperature between 41°C and 43°C. They had 6 complications: 3 bone marrow suppression, 1 leakage, 1 intestinal perforation and 1 acute renal failure. They explained bone marrow suppression with the administration of anti-cancer drugs and antibiotics; the renal failure was caused by overhydration but they did not explain the leakage and the perforation. In another study, done in 2000, Beaujard et al[36] analyzed 83 patients, who underwent HIPEC treatment, using an inflow temperature of 45°C. Two of these 83 patients had a postoperative peritonitis, due to duodenal leakage in the first case, while, in the second case, they didn't find any leak or bowel perforation at the reoperation; there is no mention of the cause that provoked the perforation.

We know that, when patients are treated with HIPEC, anastomotic leakage and adhesive ileus are the most important concerns[28]. Our study was conceived from the awareness that this risk of damage for normal tissues during the HIPEC, increases as the temperature rises[1]. We also considered that a temperature higher than 43°C may induce bowel perforation due to the ischemical changes caused by heat[31].

In this way our research on medline was done using words like "intraoperative intraperitoneal chemohyperthermia and morbidity", focusing our attention on those studies which used open technique of HIPEC and which reported morbidity like bowel obstruction, and especially like bowel perforation due to hyperthermia. We chose to focus the research on the open technique for two reasons: first of all, we know, according to Stephens et al[30], that in the closed technique we have a major risk of anastomotic leakage or digestive burns, located close to the tip of the inflow drain, where high temperatures are achieved due to the impossibility to manipulate the bowel directly. The Coliseum Technique allows the surgeon to move the Tenchoff catheter around the abdominopelvic cavity, improving the distribution of both heat and drug. We believe that this risk exists, although less frequent, even for the open technique because the abdominal cavity represents a complex and nonsystemized environment and, experiences with multiple intraperitoneal thermal probes have demonstrated the heterogeneity of the obtained temperatures[36-37]. Some studies have confirmed the existence of preferential flows inside the abdominal cavity[38-39]. Probably, this is the reason for some bowel complications as reported by various Authors[37,40]. In this way we reviewed literature from 1990, seeking any Author who wrote about the existence of a correlation, in their studies, between morbidity, especially bowel perforation, and the use of hyperthermia during intraoperative intraperitoneal chemotherapy. We have found, as result of different studies, 9 articles written about perforation, and all the 9 works used open technique.

Jacquet et al[40] analysed morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by citoreductive surgery and heated intraoperative intraperitoneal chemotherapy. Jacquet et al concluded that three clinical variables were significantly associated with morbidity and one of these is the intraabdominal temperature during the 2 hour HIPEC cycle. The other two are male sex and the duration of surgery. Besides, he noticed that the mean intraabdominal temperature during HIPEC was significantly higher in that group of patients who died. Intraabdominal temperature was a prominent factor associated with morbidity. Patients who presented postoperative complication had a higher intraabdominal temperature (41.4°C vs 40.9°C) over the 2 hour procedure.

Even Samel et al[33] found three factors that may be considered responsible for the HIPEC-related complications and two of these are thermal tissue trauma and the synergism of surgical and thermal trauma. The last one is tissue vulnerability due to advanced incurable cancer growth. We underline that the bowel perforations were most frequently located on the small bowel surfaces, extensively traumatized by the surgical resection of cancer implants; but Jacquet et al, however, had one patient who presented a small perforation in an intact (non traumatized) bowel surface area[40]. We cannot exclude it as a possible hyperthermia related complication. According to Samel et al[33] and Witkamp et al[41] the cytotoxic effect of hyperthermia is not only temperature dependent, but is also related to the exposure time and the time relation to the other therapies. In other words not only the degree of hyperthermia but even the duration of hyperthermia is a risk factor. Intraabdominal temperature, during the 2 hours cycle of HIPEC, is an important predictive factor of morbidity. According to Jacquet et al[40] the mean temperature, over 2 hours procedure, was more predictive of morbidity than the maximal temperature. A 0.5°C difference, over the 2 hour time, period may lead a more significant damage than a 0.4°C difference in peak tem-

perature. Prolonged exposure to heat may interfere with the wound healing process by denaturing intracellular proteins in fibroblasts. Mean temperature above 41°C should be avoided, particularly in elderly patients and in patients undergoing a long duration surgery (>12 hours). There is no consensus yet on the optimal temperature during HIPEC procedures. We know that the synergism between various cytotoxic drugs and hyperthermia starts at a temperatures of 39°C and it is stronger at higher temperatures. Above 43°C this synergism seems to decrease in most cytotoxic drugs and the toxicity of heat on the small bowel increases above 43°C[41]. One of the main problem with HIPEC remains the impossibility of achieving an exact intraperitoneal temperature[42]. Detroz et al[43] suggest an intraperitoneal temperature between 42 and 43°C during HIPEC; it seems to be a good rapport between the anticancer action of heat on the neoplasm residues and the respect of the intraabdominal viscera and the anastomosis. Besides, Porcheron et al[44] underline the importance of the heated solution flow rate to prevent intestinal damage and they suggest to use a flow rate of 0.9 L/min, two "inflow" drains and one "outflow" drain to obtain a better temperature homogenization in the abdominal cavity[44].

Conclusions

We believe, according to Shido et al[32], that maintaining the intraperitoneal temperature under 43°C is better to avoid thermal damage to the small intestine during perfusion in HIPEC especially in elderly patients and in patients undergoing surgery of a long duration (>12 hours)[40]. However, this review wants to focus our attention on the possible damages causing by the heat. Therefore, we need further studies to achieve an exact intraperitoneal temperature.

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