Hyperthermic Intraperitoneal Chemotherapy: Nomenclature and Modalities of Perfusion

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Following international consensus, HIPEC should be the acronym used in the scientific literature to refer to the hyperthermic intraperitoneal chemotherapy. Several modalities of perfusion are used to deliver HIPEC: open abdominal technique (Coliseum), closed abdominal technique, peritoneal cavity expander, semi-opened abdominal technique. There is no sufficient evidence in literature confirming the superiority of one technique over the others in terms of outcome, morbidity and safety to the personnel of the operating theatre. Each option has its own operational advantages and disadvantages and future prospective studies must be conducted to establish which one is the best alternative. Today, the best technique is the one which is routinely used and improved into each specialized institution involved in the management of peritoneal surface malignancy.


KEY WORDS: hyperthermia; peritoneal carcinomatosis; techniques; intraperitoneal chemotherapy

INTRODUCTION

Patients with peritoneal carcinomatosis have long been considered as a terminal condition with no curative options. Over the past decade, novel therapeutic approaches to peritoneal surface malignancies have emerged. Loco-regional treatments including cytoreductive surgery and peritoneectomy procedures for the macroscopic disease in combination with perioperative intraoperative chemotherapy for the microscopic residual disease have been developed for this loco-regional disease. There are different modalities for perioperative intraperitoneal chemotherapy administration. Most of peritoneal surface malignancy treatment centers exclusively use hyperthermic intraperitoneal chemotherapy (HIPEC), some others only early postoperative administration and others use both sequentially. Several devices or technologies of HIPEC have been described and are currently used into specialized centers. Although the use of HIPEC has gained wider acceptance, the specifics of its administration lack uniformity. Debate on the best technique for HIPEC is still open. In this review, after the report of consensus on nomenclature, the methodology, benefits, and risks associated with each technique are discussed.

Standardized Nomenclature

Multiple names and its acronyms have been used into scientific literature to refer to the intraoperative administration of hyperthermic intraperitoneal chemotherapy, often causing confusion. The Dutch group [1] proposed in 2004 during the 4th Workshop on Peritoneal Surface Malignancies held in Madrid, the use of the term “HIPEC.” The Workshop participants were already in favor of its acronym [2]. The results of the web based voting confirmed this consensus and “HIPEC” was chose by 61.29% and 78.1% of experts during the first and the second round of the vote, respectively. So this acronym should be used to refer to the hyperthermic intraperitoneal chemotherapy into scientific literature and communication.

The authors have no financial interest related to the contents of this article to disclose.

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Received 17 March 2008; Accepted 21 March 2008 DOI 10.1002/jso.21061 Published online in Wiley InterScience (www.interscience.wiley.com).
study including 504 patients with colorectal carcinomatosis treated with cytoreductive surgery combined with perioperative intraperitoneal chemotherapy [5]. Its efficacy is limited by adhesions that can result in pooling of the chemotherapeutic drugs in intraperitoneal loculations. Not only does this sequester the treatment from tumor cells, loculations also result in exposure of normal tissue to high concentrations of drug, thereby adding to the morbidity of the therapy [6].

EPIC do not involve hyperthermia. However heat has been shown to be cytotoxic in vitro at 42.5 °C [7], and hyperthermia has been shown to enhance the antitumor effect of agents such as oxapliplatin, mitomycin, doxorubicin, and cisplatin, by augmenting cytotoxicity and increasing the penetration of drugs into tissue [8–10]. Moreover, Elias et al. recently compared two groups of patients with colorectal carcinomatosis with characteristics as similar as possible. One was treated with EPIC using 5-FU and mitomycin C and one with HIPEC using oxapliplatin at 43 °C. All results were in favor of HIPEC group: mortality, morbidity, rate of peritoneal recurrence which was twice in EPIC group and overall survival [11].

Thus, EPIC may be used in the treatment of microscopic residual peritoneal disease, but following HIPEC which seems to be more efficient, with an increased risk of postoperative complications.

**HIPEC.** To take advantage of the synergistic effect of chemotherapy and hyperthermia, several different HIPEC devices to enable intraoperative perfusion of the peritoneal cavity with hyperthermic chemotherapy have been developed. Constant hyperthermia is obtained by a closed continuous circuit, with pump, heater, heat exchanger, and real-time temperature monitoring. Open circuit without recirculation and reheating of the instillate should be avoided [8,9]. To avoid systemic hyperthermia during the perfusion procedure, core temperature have to be not more than 34–35 °C at the beginning of the perfusion. Precocooling can be obtained by using cooling hat, legs or blankets. But for most of teams, it was not found to be necessary and precocooling is simply accomplished by limited use of body warming during the cytoreduction, which is often a long procedure [12]. During the procedure, temperature probes must be placed at different sites of circuit and intra-peritoneal cavity: heat generator, inflow and outflow drains, bladder, liver, mesentery [13]. It is agreed that the desirable intra-abdominal temperatures range to maintain during HIPEC is 41.5–43 °C, needing inflow temperatures at 46–48 °C [2]. The duration of the procedure varies according to investigators and drugs used from 30–120 min. An increased drug concentration in the instillate with a shorter bathing duration would probably give similar pharmacokinetic results to a longer bathing duration with decreased drug concentration. The best duration is not known and depends on the protocol used [8,9]. Among the different devices reported into scientific literature we will discuss advantages and inconvenient of open abdomen (coliseum) technique, closed abdomen technique, peritoneal cavity expander and semi-open technique.

**Open abdomen technique.** The open abdominal technique has also been referred to as the “Coliseum technique”. A silastic sheet is sutured over a Thompson retractor and to the patient’s skin over the abdominal incision. This suspends that abdominal wall creating a “Coliseum” or “soup bowl-like” container for instillation of the peritoneal perfusate. An incision is made in the middle of the sheet to allow manual manipulation of the intra-abdominal contents to prevent stasis of the heated perfusate. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure (Fig. 1).

Elias et al. [14] did a prospective phase II trial testing seven different techniques in 32 patients. They found that complete closure of the abdominal wall before the perfusion restricted the volume of the perfusion, decreased spatial diffusion of the instillate, and resulted in lack of thermal homogeneity. Use of the a peritoneal cavity expander allowed an immediate thermal homogeneity, but the expander isolated the abdominal wall from the instillate, resulting in early parietal peritoneal recurrence. The use of coliseum technique was identified into this single institution as the best technique in terms of thermal homogeneity and spatial diffusion. Because the surgeons can manipulate the intra-abdominal viscera during perfusion, all peritoneal surfaces are equally exposed to therapy. Furthermore, excessive heating of normal tissue that can exacerbate post-operative ileus and increase the incidence of postoperative perforation or fistula formation is avoided [15].

Disadvantage of this technique is that the open abdomen naturally leads to heat dissipation at the surface of the instillate, making it more difficult to achieve hyperthermia with high temperatures. It also increases exposure of operative personnel to chemotherapy. Because the surgeon is required to manually manipulate the viscera, increased potential exists for contact exposure. Moreover, despite the use of the smoke evacuator, heated chemotherapy can aerosolize, creating inhalational exposure. Stuart et al. [16] evaluated the safety of operating room personnel during the coliseum technique. All assessments (urine members, air sampled, and sterile gloves examination) were found to be in compliance with established safety standards. Since this study, no trial reported on increased risk of chemotherapy exposure. However, guidelines concerning safety considerations for operative room personnel are needed and have well established by Gonzalez-Bayon et al. [17]: selection and education of operative room personnel, restriction of personnel inside the operative room, use of rigid containers, protective barrier garments, disposable, impervious gown, high power filtration mask, smoke evacuator, avoided spills.

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>TECHNIQUE</th>
<th>NB</th>
<th>MORTALITY (%)</th>
<th>MORBIDITY (%)</th>
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<td>Sugarbaker et al. [22]</td>
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<td>9</td>
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<tr>
<td>Shen et al. [21]</td>
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<tr>
<td>Kusamura et al. [20]</td>
<td>Closed</td>
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<td>1</td>
<td>12</td>
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<tr>
<td>Glehen et al. [19]</td>
<td>Closed</td>
<td>216</td>
<td>3</td>
<td>24</td>
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**Table I.** Mortality and Morbidity Following Cytoreductive Surgery Combined With HIPEC Using Closed or Open Abdomen Techniques
hyperthermia, and goal of treatment (curative or palliative intent) comparisons of postoperative results as well as survival results between the different procedures are difficult.

**Closed abdomen technique.** The intraoperative closed technique is perhaps the most widely used method of HIPEC. The closure of the abdominal wall may be temporary or definitive. Anastomoses are performed before or after perfusion. No increased risk of anastomotic fistula or recurrence have been reported for teams which are performing their anastomoses before [19,20]. This abdominal wall may be manually agitated during the perfusion in an attempt to promote uniform heat distribution. Figure 2 illustrated the technique used in Lyon.

The major advantage of the closed technique is the ability to rapidly achieve and maintain hyperthermia, because there is minimal heat loss from the closed abdomen. The technique has been refined with modeling studies to optimize thermal homogeneity [24,25]. In addition, there is minimal contact or aerosolized exposure of the operating room staff to the chemotherapy. Moreover, intraperitoneal chemotherapy with positive pressure has been reported to enhance the penetration of drugs into tissue. It was reported in vivo by Jacquet et al. [26] for the intraperitoneal administration of doxorubicin at pressure of 20–30 mm Hg. Recently, Esquis et al. [27] reported that intraperitoneal administration of cisplatin with increased intra-abdominal pressure (40 mm Hg) improved the tumor accumulation and the antitumor effect of the drug in rats bearing advanced peritoneal carcinomatosis.

The main disadvantage of the closed technique is the lack of uniform distribution of the heated intraperitoneal chemotherapy. With the instillation of methylene blue during the procedure, uneven distribution was reported [14,15]. Inadequate circulation of heated intraperitoneal perfusate leads to pooling and accumulation of heat and chemotherapy in dependant parts of the abdomen. This may result in increased systemic absorption and result in foci of hyperthermic injury that could contribute to postoperative ileus, bowel perforation, and fistula. However, the two largest clinical trials evaluating the closed abdominal technique on more than 200 patients, the mortality and

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**Fig. 2.** HIPEC device using a closed abdomen procedure. [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]
Semi-closed (semi-opened) intraoperative
- More uniform heat distribution
- More complex apparatus
- Increased risk of OR staff exposure to chemotherapy
- Heat dissipation

Peritoneal cavity expander
- Uniform distribution of chemotherapy
- Increased risk of OR staff exposure to chemotherapy
- More complex apparatus
- Not popular

Open intraoperative
- More uniform heat distribution
- Increased risk of OR staff exposure to chemotherapy
- More complex apparatus
- Not popular

“Coliseum technique”
- More uniform drug distribution
- Heat dissipation
- More complex apparatus
- Not popular

Closed intraoperative
- Minimizes exposure of OR staff to chemotherapy
- Uneven heat distribution
- Lack of uniform drug distribution

Table II. Techniques of Intraperitoneal Chemotherapy Administration

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Early postoperative chemotherapy</td>
<td>Multiple cycles of chemotherapy</td>
<td>Increased toxicity</td>
</tr>
<tr>
<td>Closed intraoperative</td>
<td>Minimizes exposure of OR staff to chemotherapy</td>
<td>Uneven distribution of chemotherapy</td>
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<tr>
<td>Peritoneal cavity expander</td>
<td>Easier to achieve high perfusion temperatures</td>
<td>Port malfunctions</td>
</tr>
<tr>
<td>Semi-closed (semi-opened) intraoperative</td>
<td>More uniform heat distribution</td>
<td>No hyperthermia</td>
</tr>
<tr>
<td></td>
<td>More uniform drug distribution</td>
<td>Uneven heat distribution</td>
</tr>
<tr>
<td></td>
<td>Minimizes exposure of OR staff to chemotherapy</td>
<td>Lack of uniform drug distribution</td>
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A summary of the advantages and disadvantages of the above techniques are depicted in Table II.

CONSENSUS VOTE ON MODALITIES OF PERFUSION

Experts were asked to vote on the best technique of HIPEC. The results of two rounds of vote are reported in Table III. The majority thought that there is no sufficient evidence in literature to establish the superiority of one technique over the others. The only way to demonstrate it would be to conduct a prospective randomized study. Actually, each specialized team have to improve and adapt their technique (open or closed) to allow acceptable mortality and morbidity rates, low risk of staff exposure to chemotherapy and improved survival outcomes.

REFERENCES


