Hyperthermic Intraperitoneal Chemotherapy
Methodology and Safety Considerations

Santiago González-Moreno, MD, PhD, Luis González-Bayón, MD, PhD, Gloria Ortega-Pérez, MD

INTRODUCTION

Selected patients with peritoneal surface malignancies benefit from a radical therapeutic approach consisting of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy (PIC), which may be complemented by systemic chemotherapy. Numerous studies have shown the efficacy of this strategy, which has led to survival results unknown to date, even in the era of last-generation chemotherapy and biologic agents.1–3 Its clinical application is fully developed and well-established in specialized centers.4

The authors have no conflicts of interest to disclose.

KEYWORDS

• Hyperthermia • Safety • Intraperitoneal chemotherapy • Peritoneal neoplasms

KEY POINTS

• Several methods of delivering HIPEC have been described but no significant differences in treatment outcomes, morbidity, or safety have been found among them. The ultimate choice is left to individual preference or institutional criteria.
• Administration of HIPEC is safe for operating room personnel; chemotherapy exposure during the procedure is negligible provided universal precautions, individual protection measures, and environmental safety guidelines are followed.
• Proper education of operating room staff about the essentials of HIPEC and on the proper handling of chemotherapy is the first safety requirement.

INTRODUCTION

Selected patients with peritoneal surface malignancies benefit from a radical therapeutic approach consisting of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy (PIC), which may be complemented by systemic chemotherapy. Numerous studies have shown the efficacy of this strategy, which has led to survival results unknown to date, even in the era of last-generation chemotherapy and biologic agents.1–3 Its clinical application is fully developed and well-established in specialized centers.4

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a Peritoneal Surface Oncology Program, Department of Surgical Oncology, MD Anderson Cancer Center, Calle Arturo Soria 270, Madrid 28033, Spain; b Servicio de Cirugía General III, Hospital General Universitario Gregorio Marañón, C/Dr Esquerdo 46, Madrid 28007, Spain; c Universidad Complutense de Madrid, Facultad de Medicina, Plaza de Ramón y Cajal, Ciudad Universitaria, Madrid 28040, Spain; d Servicio de Cirugía General y Aparato Digestivo, Hospital Universitario de Fuenlabrada, Camino del Molino 2, Fuenlabrada, Madrid 28942, Spain; e Universidad Rey Juan Carlos, Facultad de Ciencias de la Salud, Avda, de Atenas, s/n, Alcorcón, Madrid 28922, Spain

* Corresponding author.
E-mail address: sgonzalez@mdanderson.es

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The ultimate purpose of PIC is to kill in situ microscopic cancer cells or minute tumor nodules left behind after the performance of (complete) cytoreductive surgery. The specific contribution of PIC to the oncologic outcomes observed for the combined procedure remains to be elucidated, and is currently being addressed by the ongoing French randomized trial PRODIGE-7.5

PIC may be administered with hyperthermic intraperitoneal chemotherapy (HIPEC) during the course of cytoreductive surgery, in the first 4 or 5 days after surgery in normothermic conditions (EPIC), or as a combination of both. Randomized controlled studies have not been performed to formally assess which modality of PIC is more advantageous. A few retrospective comparative studies are available showing a trend for or even an advantage for HIPEC alone over HIPEC followed by EPIC or EPIC alone, in terms of morbidity (fistula formation), although not in terms of survival,6,7 but these conclusions need to be interpreted with caution. A recent small retrospective case-control Swedish study8 reports a survival advantage of HIPEC over sequential postoperative intraperitoneal chemotherapy after complete cytoreduction in colorectal carcinomatosis. It can be stated without a doubt that HIPEC is nowadays the primary method of PIC used by every surgical team treating peritoneal surface diseases and that EPIC (combined with HIPEC or on its own) has a more limited penetration among them.

The acronym HIPEC, coined by the group from the Netherlands Cancer Institute, became the standardized nomenclature for this procedure as a result of the experts’ consensus achieved during the Fourth International Workshop on Peritoneal Surface Malignancy (Madrid, 2004).9 HIPEC combines the pharmacokinetic advantage inherent to the intracavitary delivery of certain cytotoxic drugs, which results in regional dose intensification, with the direct cytotoxic effect of hyperthermia. Hyperthermia exhibits a selective cell-killing effect in malignant cells by itself, potentiates the cytotoxic effect of certain chemotherapy agents, and enhances the tissue penetration of the administered drug.10

This article describes the different techniques in use and the technology available for the administration of HIPEC. Also reviewed are the safety features that must be taken into consideration when performing this procedure. Recommended guidelines to prevent associated occupational hazards are provided.

**HIPEC METHODS**

*Description*

HIPEC is delivered in the operating room (OR) after the cytoreductive surgical procedure is finalized if a complete cytoreduction has been achieved (CC-0/CC-1). There are two main methods for intraperitoneal administration of hyperthermic chemotherapy: open abdomen technique and closed abdomen technique. Over the years mixed methods (semiopen or semiclosed) have been reported.

The open method is usually performed by the “coliseum technique,” as described by Sugarbaker (Fig. 1).11 After the cytoreductive phase has been finalized, four closed suction drains are placed through the abdominal wall and made watertight with a 3/0 monofilament purse-string suture at the skin. These drains remain in place for the postoperative period. An inflow line is placed over the abdominal wall into the peritoneal cavity and may be secured by a silk tie at the retractor frame. A different number of temperature probes may be used for intraperitoneal temperature monitoring; at least one in the in-flow line or under the right diaphragm and another one at a distance from this point (pelvis) are used, but a more intensive monitoring may be used. Probe tips may be secured with a silk tie to the tip of the corresponding drains to prevent migration. The skin edges of the abdominal incision are suspended up to a self-retaining
retractor whose frame has previously been elevated 15 to 20 cm over the patient, thus creating an open space in the abdominal cavity. This is done by a running monofilament number 1 suture. A plastic sheet is incorporated into this suture to prevent chemotherapy solution splashing from occurring. A slit in the plastic cover is made to allow the surgeon’s double gloved hand access to the abdomen and pelvis. Impermeable gown and protection goggles are mandatory. A smoke evacuator is placed under the plastic sheet to clear chemotherapy vapors or small droplets that may be liberated during the procedure. During the 30 to 90 minutes of perfusion, all the anatomic structures within the peritoneal cavity and the laparotomy incision are uniformly exposed to heat and chemotherapy by continuous manual stirring of the perfusate performed by the surgeon.

A variation of the open technique described and mainly used in Japan uses a device called “peritoneal cavity expander” (PCE). The PCE is an acrylic cylinder containing inflow and outflow lines that is secured over the laparotomy wound. When filled with heated perfusate, the PCE can accommodate the small bowel, allowing it to float freely and be manipulated within the perfusate. After HIPEC is completed, the perfusate is drained, and the PCE is removed. Fujimura and colleagues\(^\text{12}\) and Yonemura and colleagues\(^\text{13}\) reported about HIPEC with a PCE in carcinomatosis from various malignancies. The use of the PCE is very limited (if any) at the present time and has rarely been used outside Japan. Its interest in this paper is somewhat historical.

In the closed method catheters and temperature probes are placed as described previously, but the laparotomy skin edges are sutured watertight, so that perfusion is done in a closed circuit (Fig. 2). The abdominal wall is externally agitated during
the perfusion period to promote uniform perfusate and heat distribution, because pooling of these possibly leading to subsequent morbidity is a reasonable concern in this method.14 A larger volume of perfusate is generally needed to establish the circuit compared with the open technique, and also a higher abdominal pressure is achieved during the perfusion, which may facilitate drug tissue penetration.15,16 After perfusion, the abdomen is reopened and the perfusate is evacuated. Appropriate anastomoses are performed and the abdomen is closed in the standard fashion. Other teams perform anastomoses and proceed with a definitive closure of the abdomen before HIPEC is started.

The mixed methods (semiopen or semiclosed) have been developed at a later time as an evolution of an open method, to further reduce the chance of OR staff exposure to chemotherapy and prevent heat loss. Rat and colleagues17 use a latex sheet (abdominal cavity expander) water-tight sutured to the skin edges and then secured to the retractor frame, allowing a controlled overflow of the perfusate and allowing its level to reach well above the skin edges with no spillage. A transparent methacrylate cover with a laparoscopy hand port in its center is placed over the retractor’s frame and the latex piece hermetically closing the abdominal cavity. Sugarbaker18 also reported the use of a closed acrylic device with a lid, mounted on top of the coliseum to provide perfusate containment while allowing manual access to the peritoneal cavity for manipulation.

**Comparative Analysis and Choice of HIPEC Method**

Each HIPEC method has its own advantages and disadvantages, as shown in Table 1. It should be noted that, to the authors’ knowledge, no formal prospective controlled comparison of HIPEC methods has been performed. Elias and colleagues14 performed an early phase trial in which they successively tested seven HIPEC procedures. The authors concluded that closed methods were not satisfactory and that the open technique with traction of the skin upward was superior in terms of technical feasibility, thermal homogeneity, and perfusate distribution. Ortega-Deballon and colleagues19 recently published a comparative experimental study in a small number of pigs concluding that intraperitoneal hyperthermia can be achieved with both techniques and that the open technique had higher systemic absorption and abdominal tissue penetration of chemotherapy (oxaliplatin) than the closed technique.

The panel of experts assembled for the 2006 Consensus Conference in Milan, after review of scientific evidence, discussion, and voting using the Delphi methodology,
concluded that there is no evidence to establish the superiority of one method over the others regarding patient outcomes, morbidity, or surgical staff safety. A call for future studies to definitively answer this question was made but has not been answered. Therefore, any of the methods listed previously may be used for the delivery of HIPEC.

The criteria that may be taken into consideration when choosing a HIPEC method by emerging treatment programs are mostly subjective: (1) the perceived risk of environmental chemotherapy exposure (the real risk is negligible if proper safety measures are followed, as described later); (2) concerns on possible differences in the uniform distribution of chemotherapy or heat throughout the peritoneal cavity that may result in visceral thermal injury; and (3) possible differences in dosaging and perfusate volume inherent to the closed method.

Each program should use the method that best fits its institutional needs or demands in terms of operational features, safety, and occupational hazard regulations, becoming used to deal with its own advantages and disadvantages. Safety standards and considerations for the administration of HIPEC are addressed in detail later in this article. Undoubtedly, as for any surgical technique, previous experience with one of them (eg, during a training period) has an impact on the choice; however, some teams have changed their method of choice over time, even after extensive experience with one technique.

**TECHNOLOGY FOR THE DELIVERY OF HIPEC**

Regardless of the method used, an external device that heats the chemotherapy perfusate and continuously circulates it in and out of the patient to keep a target

### Table 1

<table>
<thead>
<tr>
<th>Feature</th>
<th>Open</th>
<th>Closed</th>
<th>Mixed (semiopen/semiclosed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat and chemotherapy distribution</td>
<td>More uniform&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Uneven&lt;sup&gt;b&lt;/sup&gt;</td>
<td>More uniform&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heat dissipation</td>
<td>More&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Less&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Improved (less) compared with open&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Time to achieve target temperature</td>
<td>Longer&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Shorter&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Shorter compared with open&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Direct contact of surgeon with chemotherapy (with protection)</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk of chemotherapy exposure by operating room staff</td>
<td>Theoretically increased&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Minimized&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Minimized&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk of thermal injury</td>
<td>Minimized&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Possible&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Minimized&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Complexity in assembling</td>
<td>Some (more complex if using peritoneal cavity expander)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None&lt;sup&gt;a&lt;/sup&gt;</td>
<td>More complex (expander, metacrylate cover, hand port)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Contains possible advantages.

<sup>b</sup> Contains possible disadvantages.
temperature and volume within the peritoneal cavity is always needed. Key components of this apparatus are as follows:

- A single-use circuit tubing that incorporates in most cases a reservoir where to withdraw the perfusate in case of an emergency or keep it before the perfusion starts
- A heat source
- A heat exchanger, where the perfusate is actually heated
- A roller pump that forces the perfusate from the reservoir into the patient
- A return method from patient to reservoir, which could be a second roller pump or a vacuum source
- Several temperature monitors (heat source, heat exchanger, inflow line, various points in the peritoneal cavity)

All these components, except for the single-use circuit tubing that comes inside its own sterile box, are assembled together creating a machine. Most of these devices also incorporate a computerized continuous recording of thermal data that may be displayed in situ for monitoring during the procedure and then exported or printed with different formats. This adds security and comfortability to the procedure, avoiding the need to create written records and also allowing efficient data recording for clinical research.

The first HIPEC machines had to be improvised by putting together all these individual components, in a home-made fashion (Fig. 3). Commercially available compact HIPEC machines have been developed since the late 1990s, and the number of

![Fig. 3. Technology for the delivery of HIPEC. The former machine prototypes (A) have given way to commercially available, certified compact HIPEC devices (B). In A, two roller pumps are mounted on a metallic cart; heater apparatus and heat exchanger lie to the left of the cart. Temperature registration is manual on a paper sheet. B shows three of the devices listed in Table 2.](image-url)
companies manufacturing them has gradually increased over the years (Table 2); this may be regarded as an indirect sign of the acceptability and applicability of HIPEC in clinical practice. This was also a step forward in the regulatory field, because these machines must be approved specifically for HIPEC use by the appropriate regulatory agencies (Food and Drug Administration in the United States, bearing CE marking in Europe), which definitely addresses any institutional medicolegal concerns about the use of this technology in humans. However, availability of HIPEC machines for purchase may bring the opportunity to perform surgical treatment of peritoneal carcinomatosis in suboptimal conditions, without the appropriate training and knowledge, under the false assumption that “the machine does the work.” The peritoneal surface oncology community and these companies must work together to warn against and prevent this opportunistic approach, which may result in unacceptable morbidity and suboptimal treatment results. This would eventually bring negative connotations toward the technique, potentially questioning the efforts developed over many years.

The choice of a specific HIPEC apparatus is certainly a subjective issue. Several factors may be taken into account in this decision: ability to achieve adequate hyperthermia in a short time period, adjustable flow rate, user-friendliness, ease of assembling the circuit for the surgical support staff, easy reading and continuous registration of temperatures, availability of technical support, and pricing of the machine itself and of the disposable circuit tubing kits. Testing different options in one’s own OR is advisable before making a final decision.

In a HIPEC procedure using one of these devices the roller pump forces the chemotherapy solution into the abdomen through the inflow line and pulls it out through the drains, with a flow rate around 1 L per minute (Fig. 4). The instillate’s temperature reaches 43°C to 45°C after passing through the heat exchanger, so that the intraperitoneal fluid is maintained at 41°C to 43°C. The perfusate may be first recirculated between the reservoir and the heat exchanger so that it can be heated to an adequate temperature. At this point, full closed-circuit circulation of the perfusate in and out of the peritoneal cavity is established until a minimum intraperitoneal temperature of 41.5°C is achieved and maintained. The drug is then added to the circuit and the timer for the perfusion is started. In bidirectional chemotherapy protocols the intravenous infusion of the appropriate drugs may be started at this time point, although some authors advocate doing it 1 hour before the initiation of HIPEC.

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Country</th>
<th>Food and Drug Administration Approved</th>
<th>CE Marking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belmont Hyperthermia</td>
<td>Belmont Instrument</td>
<td>United States</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pump</td>
<td>Company</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitherm</td>
<td>EFS</td>
<td>France</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Exiper</td>
<td>Medica S.p.A.</td>
<td>Italy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Gamida Tech</td>
<td>Sunchip</td>
<td>France</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Performer</td>
<td>Rand Corporation</td>
<td>Italy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ThermoChem-HT</td>
<td>Thermasolutions</td>
<td>Netherlands/United States</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
An original alternative to the use of a closed-circuit external apparatus to deliver HIPEC has been recently described by Ortega-Deballon and colleagues,\textsuperscript{22} from Dijon. Their method uses a heat source placed directly in the peritoneal cavity. It consists of two 17-m long electric heating cables insulated with a silicon wrapping. Each cable is connected to a 24-V transformer and then to a 220-V electric outlet. One cable is distributed in the supramesocolic area and the other in the inframesocolic area and between the bowel loops. Although it has been developed and used only in an experimental pig model to date, preliminary data show a favorable safety profile with no direct heat damage to the viscera, efficacy, and technical feasibility that warrant further studies to investigate its application in the human patient. The advantages of this technology in terms of cost, operating time, and simplicity are obvious.

**SAFETY CONSIDERATIONS**

OR staff faces occupational risks daily, such as blood-borne pathogens, anesthetic gases, or radiation exposure, and are used to dealing with these risks. However, the introduction, handling, and management of chemotherapy in the OR that comes with HIPEC necessarily determine a change in surgical personnel habits and may bring a biased, unrealistic perception of added danger. As for any of the risks mentioned previously, the staff involved in the procedure must be fully aware of its meaning and associated hazards to avoid unnecessary potential health problems or an irrational opposition to their participation in the program.

**Education as a Safety Factor: Influence on Behavior**

Ignorance may be the most dangerous health risk in the OR. Appropriate education about cytoreductive surgery and HIPEC is a first, mandatory safety factor that must be observed by all personnel involved in the procedure.\textsuperscript{23} The surgical oncologist
leading the team should take responsibility to provide such education and training as needed. Monographic cancer hospitals might already have in effect educational programs for nurses and ancillary staff about chemotherapy essentials and cytotoxic drug handling procedures and guidelines; in this regard, cancer hospitals have some advantage over general hospitals.

The educational program should cover the surgical technique; the intraperitoneal chemotherapy perfusion; the cytotoxic agents used; the effects of hyperthermia on these drugs and on the patient; and the indications, rationale, and results of the procedure. Then, staff needs to be educated on routes of exposure and risks of low-dose occupational exposure to cytotoxic agents. Additionally, they should be made aware of the potential risks associated with an increased amount of surgical smoke produced during cytoreductive surgery. Finally, personnel have to be trained on how to avoid these exposure hazards and how to perform a safe procedure.

It is well known from a behavioral standpoint (Health Belief Model) that, even with the proper education, it is the individual who ultimately does or does not adhere to self-protective measures, influenced by his or her perception of susceptibility, severity, benefits, and efficacy of the barriers used.24 “Unrealistic optimism” by which healthcare workers cannot believe they will become ill as a result of hazardous exposures should be avoided.

**Surgical Smoke Exposure**

Cytoreductive surgery uses high-voltage electrosurgery for visceral dissection and resection and for the electroevaporation of tumor nodules. The amount of smoke generated during this procedure exceeds that created during a regular surgical operation (eg, for colorectal cancer).25 This fact added to the length of the operation (10–12 hours) may result in cumulative exposure. Contrary to the exposure to chemotherapy, surgical staff tends to underappreciate the risks of electrosurgical smoke and the need to use protective measures.

Just by its physical effects, surgical smoke may produce headache, nausea, and eye and respiratory tract irritation to healthcare workers in the OR. It also hampers the correct visualization of the surgical field. Surgical smoke contains ultrafine particles, whose increase in the environment is related to lung dysfunction, cardiovascular changes, and mortality. Some dangerous substances have been identified in these ultrafine particles, such as benzene, toluene, furfural, and polycyclic aromatic hydrocarbons, some of which are carcinogenic or may cause ischemic heart disease. Additionally, smoke particles can bear viable microorganisms. In a recent Swedish study the amount of ultrafine particles detected during cytoreductive surgery was comparable with that in second-hand (sidestream) smoke of cigarettes. No single or cumulative values of polycyclic aromatic hydrocarbons in this context exceeded the occupational exposure limits.25,26

Investigations done by work-safety agencies in Europe and the United States have shown that it is possible to control air contamination from electrosurgical smoke by keeping the OR well ventilated and by using at all times a smoke evacuator.27,28 Air conditioning should be continuously working throughout the surgical procedure, reaching a slightly higher air pressure in the OR in relation to the surrounding area. Filters of the air conditioner should be high-efficiency particulate air and should be verified once a month for fungal contamination. Doors should be closed during the operation with hermetic closures.23 These are usually standard OR ventilation procedures, already in effect regardless of the type of surgery.

A smoke evacuator should be ready for use from the beginning of the operation. This device must have a suction unit, an absorbent high-efficiency particulate air filter, and a disposable tube for smoke conduction with a rigid end.29 Although several options
are commercially available, this apparatus is unfortunately not among the regular equipment available in every OR. Filters have a filling indicator; they should be changed frequently, and disposed of as biologic hazardous material. The tip of the smoke evacuator tubing may be handled by the scrub nurse and kept about 5 cm from the origin of the smoke to catch every contaminating substance. Suction must work always while the smoke is being produced; synchronization of the smoke evacuator with the electrosurgical generator is of great help in this regard. Air suction with this device under the plastic sheet is also used as a protective measure during the administration of HIPEC by the coliseum technique.

Additionally, individual protective measures against surgical smoke may be used. High-power filtration mask (FFP-3) with a good fit to nose and mouth is recommended wear for personnel at the OR during cytoreduction and HIPEC. These “healthcare respirators” offer high filtration of submicron particles and protect against concentrations of solid and nonvolatile liquid particles. They do not protect against gases or vapors. It should be noted that, although included in most safety guidelines, breathing through this kind of mask is neither comfortable nor easy and some persons just cannot stand them for prolonged periods of time. The consequences of not wearing them on the health of surgical workers if smoke evacuation and adequate ventilation are reinforced have not been assessed. Additionally, because no study to date has detected chemotherapy particles in the OR air during the administration of open HIPEC the need to wear such a mask instead of a regular surgical mask is debatable. Eye protection should be worn as a mechanical barrier not just for the smoke, but also for cytostatic agents and bodily fluid exposure, as part of a universal precaution protocol.

Chemotherapy Exposure

The cytotoxic agents used in HIPEC are cell-cycle independent drugs, whose effects are amplified by heat. The drugs usually used are mitomycin C, cisplatin, doxorubicin, and oxaliplatin. During HIPEC chemotherapy is always diluted, never pure, and absolute doses of drugs are in micrograms, so that it is not possible to have a major spill (defined as <5 g or 5 mL of undiluted cytotoxic agent by the US Occupational Safety Health Administration). Although toxicity of these agents is well described for therapeutic dosages, long-term effects of prolonged, repeated occupational exposure to low doses remain unknown. For this reason, all precautions and guidelines for chemotherapy handling should be observed.

The routes of exposure to chemotherapy during HIPEC are mainly direct contact and inhalation of aerosols or vapors, because accidental injection and ingestion are to be regarded as anecdotal in this context. Direct contact of cytotoxic agent with skin or mucous membranes produces irritation or dermatitis. If absorption of drugs happens and exposure to low doses is frequent, systemic effects could theoretically be possible (bone marrow toxicity, gastrointestinal toxicity, hair loss, and so forth), but this has not been proved. Inhalation of aerosols could happen if vaporization of cytotoxic drugs induced by hyperthermia occurs. The use of the smoke evacuator under the plastic sheet during HIPEC administration using the coliseum technique or the advent of the acrylic covers used in the semiopen methods minimize this route of exposure.

Stuart and colleagues, from the United States, were the first to evaluate the safety of OR personnel during HIPEC. They administered mitomycin C using the coliseum technique. Urine from members of the operating team was assayed for chemotherapy levels. Air below and above the plastic sheet also was analyzed. Finally, sterile gloves commonly used in the OR were examined for permeability to chemotherapy. All assessments of potential exposures were found to be negative, in compliance to
established safety standards. Schmid and colleagues, from Germany, arrived at the same conclusions regarding mitomycin C detection levels and glove permeability assays. More recently, a Swedish study reported by Andréasson and colleagues during HIPEC with oxaliplatin using the coliseum technique failed to detect any platinum in the urine or blood of the surgeon or the perfusionist involved in the procedure. These studies confirm that, even in the method with a higher chance for surgical staff chemotherapy exposure, delivery of HIPEC is a safe procedure from the occupational risk standpoint provided adequate, standard protective measures are observed.

RECOMMENDED GUIDELINES FOR THE SAFE ADMINISTRATION OF HIPEC

Individual protective measures and environmental measures to minimize chemotherapy exposure during HIPEC have been described before and are summarized in Table 3. This is a list of generally recommended items but it is ultimately up to every institution and treatment program to define and reinforce their own safety guidelines. Further safety considerations include OR staff selection and health checks, the management of chemotherapy spills, and the cleaning of the OR after an HIPEC procedure.

**Staff Selection and Health Checks**

Any association between participation in an HIPEC program and the chance of future newborn congenital defects, worsening of a blood dyscrasia, or even developing any health problem in the future should be avoided. Therefore, limitations for participation in the program must be established, among them:

- Pregnant or nursing women
- History of abortions or congenital malformations
- Individuals actively pursuing pregnancy (men and women)

<table>
<thead>
<tr>
<th>Table 3 Recommendations for a safe administration of HIPEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical field</td>
</tr>
<tr>
<td>Use of impervious, disposable drapes. Do not use textile cloth</td>
</tr>
<tr>
<td>Lap pads</td>
</tr>
<tr>
<td>A correct lap pad count should be obtained before initiation of HIPEC</td>
</tr>
<tr>
<td>Operating room</td>
</tr>
<tr>
<td>Doors should be closed</td>
</tr>
<tr>
<td>Signs placed outside the operating room advising that HIPEC is in progress</td>
</tr>
<tr>
<td>Restriction of personnel circulation</td>
</tr>
<tr>
<td>Absorbent towels on the floor around surgical table for possible spills</td>
</tr>
<tr>
<td>Personal protective measures: universal precautions</td>
</tr>
<tr>
<td>Disposable impervious gown (closed front, long sleeves, and closed cuffs)</td>
</tr>
<tr>
<td>Disposable impervious shoe covers</td>
</tr>
<tr>
<td>Double powderless latex gloving, outer one elbow length; change outer glove every 30 min</td>
</tr>
<tr>
<td>Eye protection (goggles)</td>
</tr>
<tr>
<td>High-power filtration mask (FFP-3) (debatable)</td>
</tr>
<tr>
<td>Environmental measures</td>
</tr>
<tr>
<td>Proper ventilation</td>
</tr>
<tr>
<td>Smoke evacuator used continuously over surgical field (under plastic drape in coliseum technique)</td>
</tr>
<tr>
<td>Residue management</td>
</tr>
<tr>
<td>Leak-proof rigid containers labeled “cytotoxic agents” should be used for every material or bodily fluid to be discarded during or after HIPEC (and during the following 48 h)</td>
</tr>
</tbody>
</table>
- Hematologic or teratogenic disease history
- Previous chemotherapy or radiotherapy treatments
- Usual work with radiographs or radiation therapy
- Active immunosuppressive treatment
- Allergy to cytotoxic drugs or latex
- Severe dermatologic disease

Regular health checks for healthcare workers involved in the delivery of HIPEC must be performed. These should be done every 6 to 12 months, collecting information on the frequency of exposure to the procedure; any incident (eg, spillage, skin contact) during HIPEC; and new symptoms (especially in skin, mucous membranes, gastrointestinal tract, hair loss, and so forth). Blood work with at least a complete blood cell count and a biochemistry panel should be obtained. After learning all the pertinent data, an individualized assessment and follow-up instructions are to be provided.

**Management of Direct Contact with Chemotherapy or Chemotherapy Spills**

The US Occupational Safety Health Administration categorizes chemotherapy spills as small or large using a threshold of 5 g or 5 mL of undiluted cytotoxic agent. If direct contact with cytotoxic agent occurs, contaminated clothing should be removed immediately and discarded into a hazardous waste container. Affected skin should be washed immediately with mild, additive-free soap without dyes or perfumes that may interact with the cytotoxic agent. If the affected area is the eye, it should be flooded immediately with water or isotonic saline for 5 minutes. The staff member should then report the incident to the occupational health office.

A small spill should be blotted dry using absorbent pads and wiped up. The area should be washed three times with water and neutral soap. Then, the area can be cleaned in the routine manner. When clearing large spills special care should be taken to avoid creating aerosols. To clean up any kind of spill personnel should wear the protective barrier garments previously described (see Table 3), including a respirator mask for large spills.

**Cleaning up the OR after HIPEC**

Education about the meaning and risks of using chemotherapy in the OR needs to transcend to the cleaning personnel. Standard protective clothing described should be used. Special leak-proof bins should be used to discard all trash from the room. All bactericidal cleaning solutions should not be used to wash the contaminated area because they may react with the cytotoxic agents and do not inactivate them. Water with neutral soap is adequate to clean up the OR after HIPEC, performing this task three consecutive times. Seventy percent isopropilic alcohol is also safe and effective. Surgical instruments should be washed three times with water and pure soap before leaving the working area.

**SUMMARY**

HIPEC is one of the cornerstones in the curative-intent treatment of peritoneal surface malignancies. It is administered after complete cytoreductive surgery. Several methods of delivering HIPEC have been described but no significant differences in treatment outcomes, morbidity, or safety have been found among the methods. The ultimate choice is left to individual preference or institutional criteria.

Administration of HIPEC is safe for personnel working in the OR; chemotherapy exposure during the procedure is negligible provided universal precautions, individual protection measures, and environmental safety guidelines are followed. Exposure to
potentially harmful electrosurgical smoke produced during cytoreductive surgery needs to be taken into consideration. Proper education of OR staff about the essentials of HIPEC and on the proper handling of chemotherapy is mandatory.

REFERENCES


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