Safety considerations for Health care Workers involved in Cytoreductive Surgery and Perioperative chemotherapy

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Abstract The combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has gained worldwide acceptance for management of selected patients with peritoneal metastases from various cancers. Cytoreductive surgery is performed with the goal of removing all macroscopic disease and is coupled with perioperative chemotherapy (POC) in the form of HIPEC with or without EPIC (early postoperative intraperitoneal chemotherapy) to deal with the microscopic residual disease. These treatments entail the use of cytotoxic drugs in the operation theatre or in the intensive care unit where they are not commonly used and put the healthcare workers participating in the treatment at risk of exposure. CRS is performed with high voltage electrocautery generating a large amount of surgical smoke which is inhaled by the involved personnel and has potential health hazards. This article outlines the safety measures to be taken while performing CRS and POC.

Keywords Safety considerations · Cytotoxic agents · Cytoreductive surgery · HIPEC

Introduction

The combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy

(HIPEC) has proved to be effective in treating peritoneal metastases (PM) from various cancers [1]. The most common indications are pseudomyxoma peritonei and appendiceal tumors with PM, peritoneal mesothelioma, colorectal cancer with limited PM, selected patients of gastric cancer with limited PM and recurrent ovarian cancer [2–6]. Trials are underway to evaluate its role in ovarian cancer as first line and second line therapy [6]. Cytoreductive surgery is performed with the goal of completely removing all the macroscopic disease and comprises of peritonectomies and visceral resections as described by Sugarbaker [7]. CRS is coupled with perioperative chemotherapy (POC) which comprises of either HIPEC that is performed immediately after CRS with or without early postoperative intraperitoneal chemotherapy (EPIC) is performed for 3–5 days in the immediate post-operative period [8]. These treatments entail the use of cytotoxic drugs in the operation theatre or in the intensive care unit where they are not commonly used. There is a risk of exposure in several ways to these drugs to the surgical team, anesthesiologists and the operating room staff. Moreover, CRS is performed with high voltage electrocautery using pure cutting current which generates a large amount of smoke for prolonged periods. Inhalation of this smoke has health hazards. Over and above the routine safety measures and protocols followed in the operating room during surgery, some additional measures are required during CRS and POC. This article outlines the safety measures to be taken while performing CRS and POC.

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Potential Hazards of CRS and POC

During CRS and POC, it's not just the surgical and anesthesiology team but the nursing staff, technicians, perfusionists and other ancillary staff that is exposed to the potential hazards of this treatment.

Electrosurgery and surgical smoke

The electrosurgical unit (ESU) was developed by WT Bovie in 1926 and popularized by H Cushing [9]. Cytorreductive surgery is performed at high voltage using pure cutting current as described by Sugarbaker [10, 11]. When cutting (vaporization) current is used, the heat causes intracellular water to boil, the cells explode and tissues divide; coagulation (fulguration) current develops less heat, causing cell drying and thus coagulation [12]. Both these methods produce a varying degree of plume, or surgical smoke which is inhaled by the people involved in the procedure. Even when CRS is performed using a lower voltage or on coagulation mode, considerable amount of surgical smoke is produced. The average duration of surgery is long 6–12 h leading to prolonged exposure during each procedure. Inhalation of electrosurgical smoke has for long been considered a potential health hazard. Table 1 lists the potential hazards of surgical smoke.

Surgical smoke is made up of 95 % water or steam and 5 % cellular debris in the form of particulate material. The particulate matter is composed of chemicals, blood and tissue particles, viruses, and bacteria [14]. The particle size of electrosurgical smoke is 0.07 μm . The smaller the particle size, the further it can travel. Studies have shown that not just the members of the operating team standing in close proximity to generation of smoke (the surgeons performing the procedure, scrubbed nurse) but members who are at a distance from the operating table like the circulating nurse, technicians, anesthesiology team members are also affected [15]. Particles larger than 100 μm remain airborne, those 5 μm or larger get deposited in the larger airways (wall of the nose, larynx, trachea and large bronchi) while those 2 μm or smaller reach the bronchioles and alveoli and get deposited there [16, 17].

Chemical composition of electrosurgical smoke and its hazards

The various chemicals found in electrosurgical smoke are listed in Table 2 [18]. Surgical smoke can produce nausea,

Table 1 Potential hazards of electrosurgical smoke (adapted from reference 13, 18)

Hazards of Electrosurgical smoke	
Anemia	Nausea/vomiting
Airway inflammation	Asthma
Throat irritation	Pulmonary congestion
Weakness	Sneezing
Hypoxia/dizziness	Chronic bronchitis
Cardiovascular dysfunction	Emphysema
Colic	Hepatitis
Dermatitis	Carcinoma
Coughing	Lacrimation
Headaches	AIDS

headache, eye irritation, respiratory tract irritation, cardiovascular changes, obstruct visualization of the surgical field and has a bad smell [19, 20].

Electrosurgical smoke contains polycyclic aromatic hydrocarbons (PAHs) that are the result of the incomplete combustion of organic matters, some of which are carcinogenic, e.g. benzo[a]pyrene [21, 22]. Some of these compounds are also found in cigarette smoke, smoked fish and meat, traffic exhaust and wood burning all of which have carcinogenic potential [23–28]. The mutagenic potential smoke generated from electrocoagulation of one gram of tissue is equivalent to that produced by smoking six cigarettes [29]. These compounds are also known to cause ischemic heart disease, increased mortality from non-malignant lung diseases [30, 31]. Despite this body of evidence, the actual mutagenic risk to the healthcare personnel is not known [32].

Other constituent of surgical smoke

Electrosurgical smoke has also been shown to contain blood particles, viruses, and bacteria in the smoke particulate matter. This bacteria and viruses can transmit disease when present in surgical smoke but evidence to support the same is lacking except for isolated case reports [33–36].

Thus, infectious organisms and carcinogens are both found in electrosurgical smoke but the actual risk to the healthcare workers remains unknown and unproven and studies to elucidate the long term hazards of smoke exposure need to be carried out. However, there is a risk and hence measures should be taken to minimize the exposure as much as is possible [37–39].

Perioperative chemotherapy

Systemic chemotherapy is administered in the ward. Hospitals have designated rooms for mixing and preparation of chemotherapy/cytotoxic drugs to minimize the exposure to the staff involved in administering the treatment. In HIPEC a heated chemotherapy solution (1–2 l) is circulated in the peritoneal cavity for 30–90 min using a roller pump and circuit [40, 41]. During this procedure the abdomen is either kept closed (Closed technique) or open (coliseum or open technique) [42, 43]. In the open technique the surgeon manipulates the bowel loops and ensures more even distribution of the heat and chemotherapy, however, there is increase exposure of the operating room personnel due to vaporization of the drug and direct contact with it as compared to the closed method [44]. In EPIC, chemotherapy is administered through a tube inserted in the abdominal cavity during surgery, kept inside for 23 h and then allowed to drain. This is repeated for a period of 3–5 days and maybe carried out in the intensive care unit.

Table 2 Chemical in surgical smoke (adapted from Ref 18 with permission)

Chemicals in electrosurgical smoke			
Acetonitrile	3-Butenenitrile	Hexadecanoic acid	Phenol
Acetylene	Carbon monoxide	Hydrogen cyanide	Propene
Acrolein	Creosol	Indole	2-Propylene nitrile
Acrylonitrile	1-Decene	Methane	Pyridine
Alkyl benzene	2,3-Dihydro indene	3-Methyl butenal	Pyrrrole
Benzaldehyde	Ethane	6-Methyl indole	Styrene
Benzene	Ethyl benzene	4-Methyl phenol	Toluene
Benzonitrile	Ethylene	2-Methyl propanol	1-Undecene
Butadiene	Formaldehyde	Methyl pyrazine	Xylene
Butene	Furfural		

When perioperative chemotherapy is administered either in the form of HIPEC or EPIC, the drug preparation either done in the pharmacy or in the operation theatre itself. This exposes the healthcare workers involved in the process to antineoplastic agents. The commonly used antineoplastic drugs HIPEC and EPIC are mitomycin C, cisplatin, oxaliplatin, doxorubicin, paclitaxel, 5 –FU, melphelan, irinotecan and carboplatin [45].

The potential routes of exposure to cytotoxic agents are

1. Direct contact: direct contact with the skin or mucous membranes [46]
2. Inhalation: This could occur during preparation of the drug either in the pharmacy department or in the operating room itself, after drug preparation the drug can be in the air in solid or liquid particulate form. Vaporization of the drug could also occur during the hyperthermic perfusion [46].
3. Accidental injection: this is uncommon and could occur due to an accidental cut or puncture with a contaminated needle or knife.
4. Accidental ingestion: This is seldom occurs and could be due to ingestion of food or beverages contaminated by the operating room waste [46].

There is evidence in literature indicating varying degrees of contamination in the operating room during delivery of HIPEC. There is a theoretical possibility of contamination of the operating room air. A study carried out on vaporization of cytotoxic drugs showed that ifosfamide vaporizes at a temperature of 23–37 degrees Celsius whereas mitomycin, doxorubicin and cisplatin do not vaporize [47]. Environmental contamination with mitomycin was not found at 43° Celsius during HIPEC in two different studies [48, 49]. In a French study for oxaliplatin exposure by the open technique no contamination of the operating room air was detected whereas heavy contamination was found inside the surgeons gloves (when only two sets were used, not when

three sets were used), the floor near the operating table, the operating table itself and the surgeons shoes. This study concluded that the main route was direct contact with the skin or mucous membranes and this could be avoided by wearing appropriate protective clothing [50]. Four other studies carried out to test the safety of platinum agents during HIPEC drew the same conclusions [51–54]. All of the above studies have found a low risk of exposure to cytotoxic agents during HIPEC, but there is a risk nevertheless. The main route of exposure is direct or indirect skin contact which can be prevented by the use of protective equipment. No significant respiratory exposure is expected unless there is accidental production of aerosols.

Hazards of Exposure to cytotoxic agents

Exposure to cytotoxic agents has shown to cause hair loss, headaches, acute irritation and/or hypersensitivity and adverse events related to reproductive health like infertility, spontaneous abortions and congenital malformations [55, 56]. The effects have occurred at lower doses as compared to those administered to patients [55]. A meta-analysis reported increase in the rate of spontaneous abortions but not that of congenital malformations and still births [57]. Children of nurses handling chemotherapeutic drugs for a long period showed learning disabilities in another study [58]. Chemotherapeutic drugs also have neoplastic potential. The International Agency for Research on Cancer has classified substances that could be carcinogenic to humans and several chemotherapeutic drugs also appear in this list. Table 2 provides a list with the IARC classification of commonly used chemotherapeutic drugs in perioperative chemotherapy [59]. The drugs that are not classified are paclitaxel, oxaliplatin, irinotecan and carboplatin (Table 3).

The incidence of cancer arising in healthcare workers exposed to chemotherapeutic agents is unknown. There are few case reports in literature [60, 61]. There are also some

Table 3 IARC classification of chemotherapeutic drugs according to their carcinogenic potential

Group 1	Carcinogenic to human	Melphelan
Group 2 A	Probably carcinogenic to humans	Cisplatin, Doxorubicin
Group 2B	Possibly carcinogenic to humans	Mitomycin C
Group 3	Not classifiable as to its carcinogenicity to humans	5-FU
Group 4	Probably not carcinogenic to humans	

epidemiological studies that have shown an increased incidence of various cancers amongst nurses exposed to chemotherapeutic agents [62–64]. Thus, POC poses a risk of exposure to low doses of chemotherapeutic agents and though their long term effects are unknown, every effort should be made to avoid a breach in the safety measures leading to exposure.

Safety measures to be employed during CRS and POC

Safety measures for healthcare workers specific to CRS and POC were first outlined by Gonzalez-Bayon et al. in 2006 [46]. These must be employed for every procedure that is performed. The measures are summarized in Table 4.

Table 4 Safety measures to be employed during CRS and POC

Safety Measure to be employed during CRS and POC
Preparing the operating room and surgical area
Restriction of personnel
Absorbent sheets with impervious backs around the operative area to deal with spills
Protection against electrosurgical smoke
Maintaining optimal temperature, air conditioning and humidity
Maintaining optimal room ventilation
Use of local exhaust ventilation (LEV) (wall suction and smoke evacuators)
Use of personal protective equipment
Protective measures during POC
Use of personal protective equipment
Appropriate disposal of waste and handling of body fluids, blood samples and tissue specimens
Dealing with spills appropriately
Cleaning of the operating room as recommended for these procedures
Management of an exposure or personnel contamination
Maintaining spill kits
Care of health care workers involved
Appropriate selection of personnel
Education of healthcare workers
Medical surveillance

Preparing the operation room on operative area

A sign the HIPEC is in progress should be placed at the door and the entry of personnel not involved in the procedure should be restricted. Absorbent, disposable towels with impervious backs should be placed on the floor around the operating area to absorb any spillage [46].

Protection against electrosurgical smoke

- Air conditioning and humidity**

Air conditioning should be working throughout the surgical procedure, producing a slightly higher pressure in relation to the surrounding area. Doors should be closed during the operation with hermetic closures. Temperature should be 18–26 degrees Celsius and air humidity 45–60 % [13].

- General room ventilation**

The National Institute for Occupational Safety and Health (NIOSH) recommends a combination of general room ventilation and LEV (Local exhaust ventilation) as the first line of protection for controlling surgical smoke. The general room ventilation should be a high efficiency particulate air (HEPA) filter or equivalent for trapping particulates [65]. It also is important to ensure that the filters for the general ventilation system are maintained and changed as recommended by the manufacturer of the system. Dirty air filters will impede room air exchanges. The Association for periOperative Registered Nurses (AORN) recommends that operating room air exchanges should be maintained at a minimum of 15 air exchanges per hour [66]. The ASHRAE/ASHE (American Society of Heating, Refrigerating and Air-Conditioning Engineers) ventilation standard for new construction of healthcare facilities requires a minimum total air exchange rate of 20 air exchanges per hour [67]. Air inflow volume should be 15 % higher than the outflow, air speed must be lesser than 0.3 m/s [46].

- Local exhaust ventilation (LEV)**

Commonly used equipment for LEV includes wall suction and smoke evacuators. Wall suction have a much lower suction pressure as compared to smoke evacuators, hence a high plume generating procedure like CRS requires

a smoke evacuator [65]. Moreover they cannot remove particulate matter and gases and are useful only for pulling liquids. Smoke evacuators contain a suction unit (vacuum pump), filter, hose, and an inlet nozzle. The smoke evacuator should have high efficiency in airborne particle reduction and should be used in accordance with the manufacturer's recommendations to achieve maximum efficiency [65]. A capture velocity of about 100 to 150 ft per minute at the inlet nozzle is generally recommended. The smoke evacuator or room suction hose nozzle inlet must be kept within 2 in. of the surgical site to effectively capture airborne contaminants generated by these surgical devices. The smoke evacuator should be working (activated) at all times when airborne particles are produced during CRS. At the completion of the procedure all tubing, filters, and absorbers must be considered infectious waste and be disposed appropriately and new ones installed before each procedure. While there are many commercially available smoke evacuator systems to select from, all of these LEV systems must be regularly inspected and maintained to prevent possible leaks [65].

- **Personal protective equipment**

The proper selection and use of personal protective equipment (PPE) can also reduce or prevent exposure to smoke plume. Various degrees of protection are associated with different types of PPE.

Surgical and laser (high filtration) masks create a barrier that protects the wearer's face from large droplets and splashes of blood and other body fluids during medical procedures. Surgical masks generally filter particles to about 5 μm in size. High-filtration masks, also referred to as laser masks, filter particles to about 0.1 μm in size [68]. Approximately 77 % of the particulate matter in smoke is 1.1 μm and smaller [69]. Although wearing the high-filtration masks affords some respiratory protection, viral particles can be much smaller than 0.1 μm . Surgical and laser masks do not seal to the face and thereby allow contaminants to enter the worker's breathing zone through gaps between the wearer's face and the mask [68]. A mask worn loosely or worn too long is less effective. Masks should be worn snugly and changed often [70]. Eye protection should be worn as a mechanical barrier for the smoke, cytostatic agents and bodily fluid exposure, as part of a universal precaution protocol [46]. NIOSH recommends the use of properly fitted, filtering face piece respirators rather than surgical and laser masks. Filtering face piece respirators with an N95 filter class designation prevent all sizes of particles from passing through the filter media and entering the wearer's breathing zone. Even taking some face piece seal leakage around the respirator into account, a properly fitted N95 reduces the wearer's exposure against a range of very small particles (less than 1 μm) to large droplet sized particles ($> 60 \mu\text{m}$) by at least 10-fold [65].

Protective measures during POC

- **Personal protective equipment**

Protective barrier garments should be worn for all procedures involving preparation, use and disposal of chemotherapeutic drugs. All the healthcare workers should wear protective disposable impervious gowns (polyethylene-coated polypropylene are better than polypropylene alone) and shoe covers and eye wear for droplet protection [71, 72]. Double gloves should be worn by all the staff at the surgical field and for cleaning up spillages [73]. Latex powder-free gloves are recommended as powder is known to absorb cytotoxic agents and increase exposure [46, 73]. Gloves should be changed every 30 mins while constantly working with cytotoxic agents as they do not completely prevent cytotoxic drug penetration during prolonged contact [48]. One study found a much lower rate of contamination when 3 pairs of gloves were worn and hence the authors recommended routine use of 3 pairs of gloves [50]. Surgeons in direct contact with a cytotoxic agent should wear outer gloves till the elbow [46].

- **Disposal of waste and handling of specimens and blood samples**

NIOSH has laid down guidelines for handling of samples and specimens from patients receiving cytotoxic therapy as well the waste generated during its administration and the same applies to POC. Containers for waste disposal should be leak-proof and labelled appropriately. They should be emptied when they are half full and be handled minimally and gently. Any body fluid, blood sample, tissue specimen, laparotomy pads, drapes, gowns, plastic tubing, must be handled as biological hazardous material. Body fluids are considered contaminated for 48 h after last administration of chemotherapy and at times may be 72 h [74]. Labels reading "cytotoxic agent" should be used to mark every sample, specimen, or contaminated trash [46].

- **Cleaning up spills**

The occupational safety and health administration (OSHA) has defined a small spill as a spill lesser than 5 g or 5 ml of undiluted cytotoxic agent. A large spill is defined as a drop of more than 5 g or 5 ml of pure drug [75]. However since during POC the drugs are always diluted, the doses are in micrograms and major spills are not possible. The area of any spill should be washed three times with water and neutral soap and then cleaned in the routine manner. To clean up a small spill, the personnel should wear the whole protective barrier garments already described. Personnel containing the spill should wear respirator mask and standard protective clothing. They should avoid creating aerosols when cleaning large spills [46, 76].

- **Cleaning the operating room after HIPEC**

Bactericidal cleaning solutions should not be used to wash contaminated area because they may react with the

cytotoxic agents and do not inactivate them. Water with neutral soap is adequate to clean the operating room after HIPEC three consecutive times. Seventy percent isopropyl alcohol is also safe and effective. Instrument should be dealt with similarly. Standard protective clothing should be worn during the cleaning [45, 76].

- **Dealing with exposure and personnel contamination**

Contamination of protective equipment or clothing, or direct skin or eye contact should be treated by:

- Immediately removing the gloves or gown.
- Immediate cleansing of the affected skin with soap and water.
- Flooding an affected eye at an eyewash fountain or with water or isotonic eyewash designated for that purpose for at least 15 min, for eye exposure.
- Obtaining medical attention. (Protocols for emergency procedures should be maintained at the designated sites for such medical care. Medical attention should also be sought for inhalation of cytotoxic drugs in powder form.)
- Documenting the exposure in the employee's medical record [76].
- Spill Kits

Spill kits, clearly labeled, should be kept in or near preparation and administrative areas. The material safety data sheets (MSDS) include sections on emergency procedures, including appropriate personal protective equipment. The ASHP recommends that kits include: chemical splash goggles, two pairs of gloves, utility gloves, a low-permeability gown, 2 sheets (12" × 12") of absorbent material, 250-ml and 1-l spill control pillows, a "sharps" container, a small scoop to collect glass fragments, and two large waste-disposal bags for cytotoxic drugs [76].

Healthcare workers involved in CRS and POC

Selection of personnel

Whereas the surgeons and anesthesiologists cannot be selected for the procedure, there is the option of selecting other personnel participating in the procedure in a way that they avoid health problems in the future. Personnel that should be excluded from the procedure would include pregnant or nursing women, women with a history of abortions, congenital malformations or teratogenic disease; individuals actively pursuing pregnancy (women or men), those with a hematological or malignant disease history, who have previous chemotherapy or radiotherapy treatments, those working with X rays or radiation therapy, known immunosuppression, allergy to cytotoxic drugs or latex or severe dermatologic disease.

Education of the involved personnel

All personnel involved in any aspect of the handling of cytotoxic drugs (physicians, nurses, pharmacists, housekeepers, employees involved in receiving, transport or storage) must receive information and training to apprise them of the hazards of the cytotoxic drugs present in the work area [77]. This information should be provided prior to their appointment and annual refresher and training should be done.

Employee training must include at least the following elements:

- Education about the potential hazards of electrosurgical smoke and cytotoxic drugs. Both males and females should be explained the importance of avoiding exposure, especially to cytotoxic drugs in early pregnancy, to enable them to make informed decisions
- Methods and observations that may be used to detect the a breach in the safe handling practices of cytotoxic drugs and managing spills
- The physical and health hazard of the cytotoxic drugs they are dealing with.
- The measures employees can take to protect themselves from these hazards.
- Personal protective equipment to be used, not just for handling cytotoxic drugs but also protecting themselves from electrosurgical smoke
- Reporting exposure to cytotoxic agents.

Medical surveillance

Yearly or two or three yearly examinations and update of the employee's medical reproductive and exposure histories is recommended by OSHA [76]. The interval between exams is a function of the opportunity for exposure, duration of exposure, and possibly the age of the worker as well as other factors deemed important by the attending physician, guided by the worker's history. Careful documentation of an individual's routine exposure and any acute accidental exposures are made. The physical examination and laboratory studies are done as required [76].

Conclusions

Healthcare workers participating in CRS and POC are exposed to electrosurgical smoke for prolonged periods and face the risk of exposure to cytotoxic drugs, both of which have potential health hazards. Though the actual risk of such exposure and the long term consequences are not known, there is a risk and efforts should be made to minimize exposure. Appropriate selection of personnel, education of

personnel, maintaining optimal operating room environment, use of LEV and personal protective equipment can minimize the risk of such exposure and reduce the health hazards. When spills or exposure occurs, immediate and appropriate measures should be taken. All involved personnel should be under routine medical surveillance.

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