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REVIEW

Safety of Health Workers During Hyperthermic Intraperitoneal Chemotherapy Procedure

Hipertermik İntraperitoneal Kemoterapi Prosedürü Sırasında Çalışan Personel Güvenliği

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ABSTRACT

Peritoneal carcinomatosis (PC) is often considered an end-stage condition. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as the only potentially curative treatment for PC. This multimodal procedure involves aggressive multivisceral resections and peritonectomy aimed at achieving a complete cytoreduction, with no macroscopic residual tumor volume within the abdomen. After surgery, a heated chemotherapy perfusate is administered intraoperatively into the abdomen to cover all peritoneal surfaces. Thus, sufficient intraabdominal chemotherapeutic drug concentration can be achieved without systemic side effects. Hyperthermia enhances the effect of intraperitoneal chemotherapy by increasing peritoneal blood flow, by direct cytotoxic effect, and by altering the tumor microenvironment. During this procedure, the health worker is at risk of exposure to cytotoxic agents at various stages (such as through air contamination or direct contact during manipulation of perfusates or chemotherapy solutions and manipulation of objects/tissues exposed to chemotherapeutics). In addition, the use of high-voltage electrocautery during the removal of both peritoneal surfaces and tumor deposits during CRS exposes the health worker to large amounts of surgical smoke for extended periods of time. Inhalation of this smoke may pose a risk to the health-care worker. Guidelines for the safe implementation of CRS and HIPEC have not yet been established. This study summarizes the current evidence on security considerations of CRS and HIPEC management.
Keywords: Hyperthermic intraperitoneal chemotherapy, cytoreductive surgery, operating personnel safety

ÖZ

Peritoneal karsinomatoz (PK) genellikle hastalığın son evresi olarak kabul edilir. Sitoredüktif cerrahi (SRC) ve hipertermik intraperitoneal kemoterapi (HİPEK), PK'nin potansiyel tedavi yöntemi olarak ortaya çıkmıştır. Bu multimodal prosedür, karın içinde makroskopik rezidüel tümör hacmi olmaksızın tam sitoredüksiyon elde etmeyi amaçlayan agresif multivisseral rezeksiyonları ve peritonektomiyi içerir. SRC'den sonra, ısıtılmış kemoterapi peroperatif olarak tüm periton yüzeylerini kaplayacak şekilde karın içine verilir. Böylece, yeterli intraabdominal kemoterapik ilaç konsantrasyonuna, sistemik yan etkiler olmadan ulaşılır. Hipertermi, periton kan akışını artırarak, direkt sitotoksik etkiyle ve tümör mikroçevresini değiştirerek intraperitoneal kemoterapinin etkisini artırır. Bu prosedürün uygulanması esnasında sağlık çalışanı çeşitli aşamalarda (hava yoluyla, doğrudan temasla, perfüzatlara veya kemoterapi çözeltilerine temasla ve kemoterapötiklere maruz bırakılan nesnelerin/dokuların temasıyla gibi) sitotoksik ajanlara maruz kalma riski altındadır. Ayrıca SRC sırasında hem peritoneal yüzeylerin çıkarılması hem de tümör depozitlerinin yok edilmesi esnasında yüksek voltajlı elektokoter kullanımı, sağlık çalışanını uzun saatler boyunca yüksek miktarda cerrahi dumana maruz bırakır. Bu dumanın solunması sağlık çalışanı için bir risk teşkil edebilir. SRC ve HİPEK'in güvenli bir şekilde uygulanması için kılavuz ilkeler henüz oluşturulmamıştır. Bu çalışma, SRC ve HİPEK yönetiminin güvenlik hususlarına ilişkin mevcut kanıtları özetlemektedir.
Anahtar Kelimeler: Hipertermik intraperitoneal kemoterapi, sitoredüktif cerrahi, personel güvenliği

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Introduction

In 1980s starting with Spratt et al.[1,2] and gaining popularity with Sugarbaker et al.[3] combined applications of "cytoreductive surgery" (CRS) and "hyperthermic intraperitoneal chemotherapy" (HIPEC) have been introduced as a new approach of operating theatre. By the introduction of this treatment modality, peritoneal carcinomatosis (PC) from colorectal cancer, has been regarded as a terminal disease manifestation with dismal prognosis and a median life expectancy ranging between 5.2 and 7 months after systemic 5-fluorouracil-based chemotherapy.[4,5] With this approach, encouraging results with a median survival time reaching 5 years and 5-year survival as high as 50% have been reported in selected patients.[6] For mucinous appendiceal neoplasms, if the PC index (PCI) is less then 20, this noninvasive malignancy has an excellent prognosis of 94% at 20 years when treated with CRS and HIPEC.[7] However, if the adenomucinosis can be completely removed, even though the extent of tumor is great, the survival is 64% at 20 years. At the beginning while this approach had been used in only limited numbers of clinical settings, especially over the last decade it has become a commonly used technique in all over the world and new surgery settings has been added every year.

The main purpose of HIPEC used with CRS is to remove the visible macroscopic disease with complete cytoreduction and to eliminate any microscopic traces of disease left behind with HIPEC. To reach this goal, the surgeon and the surgical staff are very frequently apt to staying in the same operating room for very long duration. High intensity usage of electrocautery during CRS and administration of chemotherapy drugs during HIPEC are the major risk-inducing factors. The repeated inhalation of the electrocoagulation smoke and evaporated cytotoxic agents for long periods of time may have detrimental effects on the surgeons and the personnel. Particularly cytotoxic agents are rarely to be inhaled by surgery theatre staff. In the consideration of such marathon surgeries taking about 6-12 hours long, it is obvious that the following factors such as distractibility, exhaustion, and inability in shifting the staff increase the risk.

Surgical theaters are settings with detailed safety procedures which may cause serious and dramatic results in case of ignoring them. New risks concomitant to CRS and HIPEC procedures can be induced, and related safety issues become highly important in such settings. This chapter is focused on additional safety complications that medical staff expose during the administrations of CRS and HIPEC rather than general safety issues of patients and surgery theater.

Risks and Precautions of Excessive Surgical Smoke

It is well known that a complete cytoreduction is the main purpose of this treatment. High voltage electrocautery (200-300 W) is utilized during CRS both for removing peritoneal surfaces (small intestine, intestinal mucosa, Glisson's capsule, diaphragmatic peritoneum, etc.)[8] or destroying the tumor deposits on site.[9] Besides removing the tumor nodules, the high voltage electrocoagulation is used for avoiding bleeding, as well. For this purpose, the tumors are cauterized with 3 mm ball-tipped and 10-15 cm shafted electrocautery blades,[10] during which substantial amount of smoke is inevitably produced. Such intensive smoke with its irritant bad smell may obscure the visualization of the operative field, and influences the surgical team and particularly the surgeon negatively. The exposure time of surgical smoke and thus its risks are increased due to long duration surgical process. Surgical smoke contains 95% water, 5% organic and inorganic mixtures, particulate (innominate particles) and bacteria.[11] Organic mixtures contain benzene, toluene, formaldehyde, cyanide hydroxide and aromatic hydrocarbons. In the study of Choi et al.[12], 52 different organic contents are determined which are dangerous substances when inhaled by the surgeons and the staff. Inorganic contents are composed of the by-products of organic contents such as CO_2, NO_2, and SO_2. Surgical smoke contains particles with diameters between 0.001-200 micron. Particles with the size of 0.005-5.0 microns in diameter have ability to reach to the alveolus when inhaled. Those which have the ability to reach to the alveolus are called "respiratory particles".[13]

Microorganisms take place in the smoke, too, and are comprised of bacteria, mycobacteria, fungus and viruses. Particularly due to containing respiratory particles, the surgical smoke may cause nausea, vomiting, light-headedness, irritation in the eyes, and respiratory complications. Long duration exposure to benzene may cause anemia and some other blood disorders.[14,15] Consequently, the surgical smoke poses environmental health risk for both surgeons and the medical staff.[16,17,18] Yet, it has not been proven that it is mutagenic.[19] In addition, it is unignorable that the surgical smoke may have carcinogenic effects due to the long term and continuous exposure, and its accumulated effects. Potential dangerous effects of surgical smoke are given in Table 1.[20]

Potential risks of electrocautery are less than usage of laser as well as its infectivity is proven.[21] The mutagenic effects of surgical smoke are almost as same as cigarette smoke.[22] Such mutagenicity depends on the character of ablated tissue.[23] Benzene has been proposed to be highly responsible for the mutagenicity of the electrocautery smoke. The mutagenic effect created by thermal destruction of 1 g of tissue is equivalent to that of three cigarettes.

In their study Andréasson et al.[9] evaluated the amount of particles generated during extensive surgery. The average

Table 1. Risks of surgical smoke[15,16]

Acute and chronic inflammatory changes in respiratory tract (emphysema, asthma, chronic bronchitis)
Hypoxia/dizziness
Eye irritation
Nausea/vomiting
Headache
Sneezing
Weakness
Lightheadedness
Carcinoma
Dermatitis
Dermatitis
Cardiovascular dysfunction
Throat irritation
Lacrimation
Colic pain
Anxiety
Anemia
Leukemia
Nasopharyngeal lesions
Human immunodeficiency virus
Hepatitis

surgical duration of peritonectomy group, which consisted of patients with a mean score of 14 PCI, was 9.1 hours. The control group was operated on with standard carcinoma techniques, and the average surgical time was 3.3 hours. A smoke evacuation system was used for evacuating the smoke generated during the electrosurgical procedures. Approximately half of the cases in peritonectomy group used high-efficiency particulate air (HEPA)-filter while others did not. The smoke evacuator was connected to the electrocoagulator's handpiece, and aspirated the smoke from a distance of 5 cm from the blade. In the control group, ERBE's suction device was used for electrocautery at a standard level (50-70 W). Stationary source samplers were placed 2-3 cm away from breathing zone of the surgeon, and source samplers were located 3 m away from where the electrocautery worked, and 3 m away from smoke evacuation device. The "P-Trak ultrafine particle (UFP) counter" was used to count the number of particles. At the end of evaluation, it was determined that UFP values were significantly high and HEPA-filter did not reduce the level of UFP in the peritonectomy group. The cumulative level of UFP at personal sampling counter was found higher than that of stationary sampling counter. This meant that surgical theater was exposed to high levels of UFP during long peritonectomy procedures. The surgeon himself or herself was exposed even higher levels of toxic UFP. Further in their study, Andréasson et al.[9], remeasured the UFP levels in the peritonectomy group, in whom a wider suction device was used. Contrarily, a slimmer suction device was used in the control group. As the results were examined and compared, the suction performance was effective at a rate of 60% in the control group while it was 100% effective in the peritonectomy group. Heinsohn and Jewett[24] stated that, 0.07 µm of UFP was generated from electrosurgical pencil activity, and that size was sufficiently small for them to pass through alveolus into the cardiovascular systems. Standard surgical masks can not filter particles at such small size[25,26,27,28] while can prevent particles larger than 5 µm.[29] Nowadays there are surgical masks for >0.1 µm particles. But it should be noticed they make high resistance against respiration or may cause different health risks although there are many guidelines recommending them. Such masks are not comfortable and irritating during long operations. High-power filtration masks which filter only solid and non-volatile liquid particles at submicron levels are recommended for HIPEC procedures in operating rooms.[30] However, they have no protection against gases and vapor.

What sort of solutions can be offered as long as electrocautery smokes during CRS procedures are unavoidable? In general guidelines, it is suggested that operating rooms should be well ventilated and smoke evacuators should be used at all times.[31,32,33] Air conditioning should be working during surgical procedures, and air pressure should be provided to reach to a higher level inside the theater than outside. Doors of surgery theatre should be hermetic and kept closed during the operation.[9] Those are the standard procedures for safe surgery that should be applied in all hospitals. A high standard air conditioning equipped in an operating room is very important, and much beneficial to surgical environment independent from the operation. A high efficiency filtration system to filter particles should be installed, and monthly detection of fungal contamination should be performed. Smoke evacuator including a suction unit, high efficiency particulate-absorbent air filter and disposal tube for smoke conduction with rigid end should be made ready before surgery.[33] Due to the risk of accumulation of biological material, these filters should be cleaned or changed more often. Smoke evacuator should be up to 5 cm close to the point of smoke generation. If it is placed too far away, only 50% of the smoke will be evacuated.[34,35] Suction should be performed during all the procedures. Unfortunately, such devices may not be available in every operating room.

Risks Associated with Chemotherapeutic Agents

The surgical staff's exposure to chemotherapeutic agents during the administration of HIPEC is a small risk if not at all. Normally, the chemotherapeutic solutions used in this procedure are prepared by hospital pharmacists or oncology nurses at recommended doses within the required health and safety measures. All staff and nurses taking charge in preparation of these solutions are normally well educated and experienced in this field. However, in operating rooms surgeons and other medical staff using chemotherapy agents may not be enough experienced. Chemotherapy solutions should be brought to theatre as ready-made. Solutions in the light-protected bags should be controlled for any leakage. In case of any problem it should be sent back to the pharmacy immediately. If it is suitable for use it should be delivered to perfusionist.

According to the technique of HIPEC utilized during administration, the exposure degree of perfusionist, surgeon, nurse and other assisting staff to cytotoxic agents change. Procedures have potential risks. There are 3 different methods of administrating HIPEC: Open abdomen (coliseum technique), closed abdomen technique, and peritoneal expander devices technique.[36] Laparoscopic HIPEC administration is another technique particularly used in intractable ascites treatment for palliative purposes.[37,38]

Open HIPEC methods have the highest exposure risk to cytotoxic agents. In this technique, as the CRS is completed, the abdominal cavity is flushed with heated chemotherapy. Surgeon distributes the perfused solution in all abdominal compartments with gentle movements for about 90 minutes. He provides the solution to reach on organs and all cavities. Although this procedure is applied appropriately with watertight technology during the application, some leakages may occur causing evaporation of cytotoxic agents which is dangerous for surgeon when inhaled and contacted to skin or eyes.

Mitomycin C, cisplatin, doxorubicin and oxaliplatin are the most common agents used in HIPEC administrations. Those are diluted agents and their pure chemotherapeutic forms never be used in such procedures. Cytotoxic properties of these agents are well known. However, in low dose applications due to continuous and recurrent skin exposures, the long-term risks for health care workers have not been defined yet. Therefore, related guidelines should be applied together with required precautions.[11]

Direct exposure to chemotherapeutic agents through injection or ingestion during the administration of HIPEC is a rare case. It is often with the skin exposure or inhalation. Skin or mucous membrane exposure may cause irritation or dermatitis. In case of absorption many systemic effects can be seen such as bone marrow toxicity and gastrointestinal toxicity. However, such side effects are not likely to be seen at lower and diluted doses. In the course of open HIPEC most probable exposure is inhalation of cytotoxic agents which can be prevented with the usage of an efficient smoke evacuator placed under plastic sheet.

There are clinical and experimental studies related with the subject. In a setting of a HIPEC administration with mitomycin C utilizing air sampling method, Stuart et al.[39] analyzed the urine samples of surgeons and perfusionists. During the operations, some basic precautions were taken by using smoke evacuator with large bore tube, wearing double gloves, and protecting eyes by goggles. Air samplings were placed 5 cm from the smoke evacuator and next to surgeon's mask (35 cm away from surgical site). Additional samplings were performed by smoke evacuation system. The penetration of chemotherapy agents through sterile gloves was also evaluated. As a result, mitomycin C was not determined in the urine samples of surgeons and perfusionists. Any harmful cytotoxic agent was not found in air samplings, as well. It was concluded that the use of smoke evacuator is a sufficient precaution. In the evaluation among three different kinds of latex gloves (Ultrafree®, Protegrity®, Biogel®) the most effective one in preventing the penetration of mitomycin C agent was Biogel.

In a study Kushnir et al.[40] invited surgeons to participate in a mock demonstration of intra-operative intraperitoneal chemotherapy administration. Cisplatin was used as chemotherapy agent. In an operating theatre equipped with HEPA filtration, surgeons mixed for 25 minutes a prepared solution in a metal container assumed to be abdominal cavity. Air samplings were performed from surgeon's mask and general theatre air. The penetration of chemotherapy agent through double gloves (Biogel®) was evaluated. Samples were taken from theatre floor and surgical instruments including those of cleaning and sterilization processes after operation. At the end of the study, they could not trace any cisplatin at anyone of the samples. Kushnir et al.[40] concluded that this result has justified that intraperitoneal chemotherapy could be administrated safely with educated staff by taking sufficient precautions. A major drawback of this study was that heated chemotherapy was not used which might create minimal evaporation effects. Another deficient side of it was that the duration of mixing procedure was only 25 minutes.

Schmid et al.[41] used mitomycin C agent in their study for the research of toxicity and its side effects. They also took serum samples from surgeons. Double gloves were used in the study (Biogel® and Z+® PLUS), and in every 30 minutes time outer gloves were changed. After analysis of air sampling from surgical theater, serum samples and samples from hands; no cytotoxic agent was detected. As a result of their study Schmid et al.[41] suggested that surgeons contacting

with cytotoxic agent during the administration of HIPEC are not at any risk. It can also be said for the ambient air and biological monitorization. Wearing double gloves (natural rubber latex) will be sufficient for protection.

During the application of closed method, there is no evaporation and inhalation risk. There is only a risk of leakage from closed abdominal wall or through drains. Therefore, either the surgeon closes the abdominal wall temporarily or permanently, he should be sure about that it is leak-proof by checking wound and drain holes carefully. If surgeon determines any leakage, additional sutures are necessary to take it under control. Diameter of drain's inlet pipe should be as wide as the drain diameter in order to prevent leakage.

Staff Selection

In addition to the surgical risks we mentioned above; processes such as preparation of solution, disposal of waste at the end of operation, and cleaning of released or disseminated waste if any, are also important. Usually assistant health care personnel or technicians carry out such procedures. Therefore, the selection and education of medical staff is the major point of safety. In our own practices, the prescribed chemotherapeutic agent solutions are prepared and delivered by pharmacist or a skilled and experienced nurse in medical oncology. HIPEC devices and gadgets in the operating rooms are set in place by trained technicians. Surgical nurses should be well experienced and it is advantageous to work with the same team in all operations to minimize the potential risks of spillage, skin and mucous membrane contamination, evaporation and eventual inhalation.

Another significant criterion for selection of staff is the health condition of staff. In Table 2, limitations in staff selection for participation in HIPEC procedure is shown.[29] Medical check-up of working staff in every 6-12 months is recommended in the point of evaluating cumulative side effects. Particularly any staff exposed to contact of solution due to a leak or spill, and has consequent symptoms such as atrichia, dermatitis, gastrointestinal system or mucous membrane problems should be evaluated with their complete blood count and basic biochemical observations.

Table 2. Staff Selection: Limitations for participating in the cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedures[31]

Pregnancy or nursing
History of abortions or congenital malformations
Individuals actively pursuing pregnancy
Hematologic or teratogenic diseases
History of previous chemo or radiotherapy treatments
Radiology or radiotherapy staff
Active immunosuppressive treatment
Allergy to cytotoxic drugs or latex
Severe dermatologic disease

Measures for Spills of Chemotherapy Solution or Recommendations for Treatment of After Direct Contact

All personnel should be careful at maximum and take all measures against any spills or direct contact. In case of a direct contact with any cytotoxic agent contaminated cloths should be taken off and put in the waste container. If it is a skin contact exposure area should be washed with an uncolored and odor-free soap. Interaction of cytotoxic agents and chemicals in perfumes or colors may increase the effects. If it is an eye contact, exposure area should be washed with water or saline water for 5-10 minutes. All accidents should be reported absolutely.

Spilling of small amounts on floor should be cleaned first with a dry and absorbing cloth 2-3 times and then washed with water and neutral detergent. Aerosol effects should be prevented particularly in large amount of spilling. Cleaning staff should wear waterproof galosh, protective garment, goggles and respiratory masks.

During the application of open technical risks for spilling, contamination to surgeon and medical staff, and contacting the solution to skin or eyes are more possible and potential. In the process of closed technique skin or eyes exposure can occur due to spills from drainage or wound. Technicians or other medical staff can expose to spilling solution while inserting the solution in HIPEC device or separating drainage from abdominal after the process. All procedures require high attention. In open technique for protection, double latex powder free gloves should be worn the outer one with long gauntlets (elbow length).[39]

Disposable surgical covers are preferred instead of textile products. Surgeons, nurses and technicians are recommended to use protective goggles. In closed technique medical staff should wear waterproof garment, protective goggles, double gloves waterproof shoe cover and standard masks during the procedures of HIPEC (Figure 1). In Table 3 protective measures for medical staff are given. Prepared solutions containing chemotherapeutic agents used in HIPEC procedures are not pure and quite diluted which decrease the contamination risk.

At the end of the operation, the surgical theaters are washed three times with neutral water and detergent. Standard bactericidal solutions are not recommended for the possibility of their interaction with cytotoxic agents.

Table 3. Protective measures for surgical staff in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedures

Disposable impervious gown (closed front, long sleeves, and closed cuffs)
Disposable impervious shoe covers
Double powderless latex gloving, outer one elbow length; change outer glove every 30 min.
Eye protector glasses
Standard OR masks (some authors advocate the use of high-power filtration mask)

Table 4. Check-list for personnel safety during hyperthermic intraperitoneal chemotherapy procedure

The selective and eduction of medical saff is the major point of safety
Check-up of working staff every 6-12 months
Prepare the chemotherapeutic solution by hospital pharmacist or medical nurses
Bring the solutions to theatre as ready-made
Controll the solutions for any leackage
Presence of high quality of ventilation system
Doors should be hermetic and kept closed during surgery
Use smoke evacuatorsystem with a HEPA-filter
Use personal protective equipment (disposable surgical covers, double gloves, goggles, high level filtering masks…)
In any contact condition, wash with water
Store waste in a rigid, sealed cantainer
At the end, wash operation rooms and surgical equipments three times with neutral water and detergent

HEPA: High-efficiency particulate air

Isopropyl alcohol (at a concentration of 70%) is also effective for this purpose. Surgical instruments are washed 3 times with neutral water and pure detergent before carrying out from the surgical theater.

There are some additional points to consider in surgical theater. Surgical theatre should be equipped with a sufficient air conditioning system and doors are kept closed at all times. Except from authorized personnel, entrances should be restricted. Absorbing towels or covers are kept around operating table in case for possible spillages. Waste containers are used to collect HIPEC solution bags and other waste products.

As a result, the administration of HIPEC introduces medical staff additional risks. However, those risks can be minimized by taking some professional measures. Selection of well-trained medical staff, presence of high quality air ventilation system in the operating rooms, and the use of protective equipment such as double gloves, goggles, and protective surgical gown are important measures. Shortly, exposure risk is not really threatening if guidelines are applied with high care and attention. Closed HIPEC administration is much safer for medical staff. There is a check-list for personnel safety during HIPEC procedure at Table 4.

Figure 1. Staff clothing in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedures appropriate to safety measures

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.T., Z.M., Concept: K.T., Design: K.T., Data Collection or Processing: K.T., Z.M., T.B., Analysis or Interpretation: K.T., Z.M., T.B., Literature Search: K.T., Z.M., T.B., Writing: K.T., Z.M., T.B.

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