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Is hyperthermic intraperitoneal chemotherapy (HIPEC) safe for healthcare workers?

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ABSTRACT

Background: During hyperthermic intraperitoneal chemotherapy (HIPEC), caregivers are exposed by different routes to cytotoxic drugs. This review proposes an overview of the safety of HIPEC by assessing existing data on protection procedures, biological and non-biological samples. Based on these data, relevant good practices, eventual irrelevant overprotection procedures and missing data to implement adapted protections are highlighted.
Materials and methods: Data were extracted from a systematic review of literature from 1980 till 2016: number and type of surgical procedure, healthcare professionals present, protective equipment, samples, pre-analytical method and analytical method.
Results and discussion: Only 55 HIPEC procedures have been evaluated. The majority of antineoplastic drugs used have all required characteristics to penetrate the organism and are recognized as very dangerous. Moreover, a great heterogeneity in protective equipment used, either individual or collective is observed. Environmental contamination occurs during HIPEC, especially for all surfaces in the operating room. Compounds penetration into caregivers lungs cannot be excluded. Priority remains to prove professionals contamination by focusing on biological samples. Biological material is rarely sampled or samples are not necessarily adapted.
Conclusion: Repeated blood tests should be preferred using appropriate sampling schedules and validated sensitive analytical methods. Furthermore, there is a great need of new biological indicators to monitor caregivers exposure.
During hyperthermic intraperitoneal chemotherapy (HIPEC), healthcare workers are exposed by different routes to cytotoxic drugs. There are currently few available occupational exposure data and environmental monitoring and biomonitoring must be improved in order to ensure optimal protection against antineoplastic drugs.

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1. Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) began to be performed in the 1980s in the United States, Japan and France [1–3]. Indications for this technique are peritoneal carcinomatosis due to macroscopic primary malignancies such as mesothelioma and pseudomyxoma but especially peritoneal secondary tumors, mainly from colorectal cancer [4]. HIPEC is still being evaluated for secondary origin of gastric, pancreatic or ovarian tumors [5,6].

HIPEC is preceded by a first step of surgical resection and maximal cytoreductive surgery (CRS) to remove any gross lesions [7]. However, surgery leaves in abdominal cavity and viscera some microscopic residual disease, and systemic chemotherapy is generally not effective because of low drug penetration [8]. The technique then consists in administering cytotoxic drugs directly into the abdominal cavity. A bath of cytotoxic drugs diluted in solvent: dextrose 5% or saline solution is injected in the abdominal cavity and heated to 42 ± 1 °C for a period of 30–90 min according to the protocol [8]. Surgeon manipulates the viscera in order to allow homogeneous penetration of the cytotoxic drugs into the abdominal cavity and between organs. This concept combines activity of chemotherapy with hyperthermia, allowing cytotoxic activity either at molecular, cellular or tissue levels [9]. This immediate administration of cytotoxic drugs allows treating the residual subclinical disease before tumour cells are trapped by fibrin deposition and adhesions [10]. Almost an exclusively local cytotoxic effect is observed thanks to the impermeability of the peritoneal-plasma barrier [11]. Nevertheless, a concentration gradient ranging from 20 to 1000 is obtained through the first 3 mm of tissues, depending on the cytotoxic drug used [12]. Drugs classically used are platinum complexes, mitomycin C (MMC), irinotecan, docetaxel and paclitaxel, but the best drug to use for HIPEC is still unknown today [13–15]. This surgery can be performed either using closed-abdomen or open-abdomen HIPEC techniques. The latter is called “coliseum technique” as described by Sugarbaker [11]. This most common technique allows an improvement of cytotoxic biodistribution and is also preferred by surgeons because the anastomosis is performed after HIPEC [16–18]. However, the environmental and healthcare workers contamination risk is increased and makes HIPEC the riskiest surgical technique for surgical teams [19–26]. Antineoplastic drugs exposition is a major problem for caregivers' health, because there is a growing scientific evidence demonstrating an excess of cancer in exposed populations [27,28].

During HIPEC, healthcare workers in the operating room are exposed by different routes to cytotoxic drugs. Among them, the surgeon is the most exposed. Main exposition sources are the generation of vapors, aerosols and chemotherapy projections of droplets or leakage, causing risks of passage through protective masks and also a potential deposit on skin remained unprotected (neck, forehead) [29]. Another contamination source to take into account is the contact with surfaces and materials, mainly involving cleaning technicians [30].

The toxicity of antioneoplastic agents used in these HIPEC techniques is recognized either for the platinum complexes (cisplatin rated carcinogenic, mutagenic, reprotoxic (CMR) 2A) or irinotecan, despite the absence of evaluation by International Agency for Research on Cancer (IARC) [31].

Over the last few decades, number of publications about patient outcomes has highly increased [32,33], but few data are published on the toxicity of molecules used during HIPEC. To date, no specific recommendation to the management and risk prevention of environmental contamination in healthcare centers, is published.

Caregivers exposure monitoring is typically provided by a routinely performed medical supervision. However, these tests often detect risks too late, after declaration of the pathology. A biological monitoring can also be accomplished by indirect methods like the Ames test, the sister chromatid exchange studies, but these methods are limited in terms of specificity and sensitivity [34–36]. Many research teams have preferred to assess healthcare professionals exposure by direct methods to detect traces of antineoplastic drugs or their metabolites in blood or urine samples [37]. Despite the specificity and sensitivity of these tests, they cannot detect the effects of long-term repeated exposures of caregivers to low doses of multiple compounds. Furthermore, many data are missing in order to claim or deny with certainty a risk to the exposed professional: relationship between the exposure dose and toxicity, difficulty to assess and differentiate the effect of low doses and exposure peaks, no threshold dose, under-reporting of occupational diseases, many confounding risk factors, incomplete traceability of caregivers' exposure and lack of post-activity follow-up. Regarding these elements, any exposure should be avoided, even at very low concentrations all along the professional life. This justifies the need to simultaneously determine traces of several chemotherapy in the environment and in the caregiver body.

The aim of this review is to make an overview of the safety of HIPEC. In this objective, existing data on applied protection procedures during HIPEC, on biological and non-biological samples will be assessed. Based on the analysis of this data, relevant good practices, eventual irrelevant overprotection procedures and missing data to implement adapted protections will be highlighted.