Hypothesis: In cases of peritoneal carcinomatosis, continuous hyperthermic peritoneal perfusion chemotherapy (CHPPC) accomplishes homogeneous distribution of the drug and heat to the entire peritoneal cavity and exposure of the visceral and parietal surfaces to the perfusate. A new closed technique for expansion that produces artificial ascites is safer for medical personnel because of less heat and drug loss and more efficacious in its hemodynamic effect on the patient.

Design: Prospective study.

Setting: University hospital.

Patients: Twenty-one patients with peritoneal carcinomatosis.

Interventions: We performed 23 continuous hyperthermic peritoneal perfusion chemotherapy (CHPPC) procedures with peritoneal cavity expansion to an intra-abdominal pressure up to 26 mm Hg, using artificially produced ascites with 4 to 9 L normal saline solution.

Main Outcome Measures: Intraoperative and postoperative complications and hemodynamic changes during CHPPC.

Results: No intraoperative complications were recorded. The artificially produced ascites did not cause significant hemodynamic changes. During the immediate postoperative period, 1 patient died of intra-abdominal hemorrhage and leakage of a colorectal anastomosis, resulting in a mortality rate of 4% in our series. Minor complications were seen in 14 patients. The complications were not attributable to the expansion technique.

Conclusions: Our proposed modification of closed-circuit CHPPC appears to be well tolerated and safe in patients with a high tumor load, as well as for the theater personnel. It remains to be investigated whether the theoretical advantages of the proposed technique will also lead to better long-term results.

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Continuous hyperthermic peritoneal perfusion chemotherapy (CHPPC) is a new mode of regional chemotherapy used for the treatment of malignant neoplasms with peritoneal dissemination. For optimal results, the temperature must be raised evenly in all compartments of the peritoneal cavity, and the entire serosal surface of the abdominal organs and the peritoneum must be exposed to the perfusate. To achieve this, many investigators have attempted the expansion of the peritoneal cavity using a peritoneal cavity expander.1,2 We herein describe a new method of peritoneal cavity expansion, using artificially produced ascites intraoperatively in a closed system of continuous perfusion, and we report on the feasibility and safety of this technique tested in 23 cases.

RESULTS

During most of the perfusion time, the temperatures measured at the mesenteric root and the outflow drain were equal, from 41°C to 43°C, and slightly lower than at the inflow drains, giving strong support to a homogeneous heat and drug exposure in a economically efficient model.

The hemodynamic effects of artificial ascites and hyperthermia on our patients are demonstrated in Figure 2 and Figure 3.

There were no intraoperative complications. Minor postoperative complications were seen in 14 cases, including wound complications (n = 7), atrial fibrillation (n = 3), transient grade II acute renal insufficiency (n = 2), grades I and II...
PATIENTS AND METHODS

From June 1, 1995, to November 30, 1997, 21 patients with peritoneal carcinomatosis with no evidence of extra-abdominal and parenchymal metastases were entered into a phase I study for cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. The protocol was approved by the local ethics committee, and informed consent was obtained from all patients. Those 21 patients underwent 23 CHPPC procedures for peritoneal carcinomatosis caused mainly by gynecological malignant neoplasms. In 3 cases, the primary tumor was of colonic origin, whereas 1 treatment was for diffuse malignant mesothelioma. Twenty patients were women and 1 patient was a man, ranging in age from 42 to 80 years (mean, 65 years).

Our modification of the CHPPC technique is described below. The abdomen is approached through a median xiphoid-pubic incision. Comprehensive adhesiolysis is performed. The primary tumor is excised, if still present, and all visceral or parietal peritoneal surface tumor deposits are removed as completely as possible. If a deposit is infiltrating deeply into an organ, and it is impossible to peel the malignant neoplasm from the surface, the involved organ or a segment of it is excised.

The intraoperative hyperthermic chemotherapy is started immediately after surgery. Two 22F silicone arterial perfusion canulae (William Harvey R15600B; BARD, Tewksbury, Mass) are placed in the right and left subphrenic spaces for infusion, and 1 silicone-filtered sump drain catheter (Axiom Traum; Axiom Medical Inc, Randolph, Calif) is placed in the Douglas pouch for drainage of perfusion fluid through separate stump wounds. Through the air vents of the sump drain, 1 temperature probe and 1 pressure probe are introduced into the peritoneal cavity and placed at the root of the mesentry. The closed perfusion system (Figure 1) is filled with 4 to 9 L isotonic sodium chloride solution, in most cases approximately 3.5 L/m² body surface area, resulting in a mean intra-abdominal pressure of 12 to 26 mm Hg. The pump system is started, and the circulating perfusate is heated. When the intraperitoneal temperature reaches 41°C, the chosen chemotherapeutic drugs are administered. Cisplatin, 80 to 120 mg/m² body surface area, was used in malignant neoplasms of the digestive tract and previously untreated gynecological malignant neoplasms, whereas docetaxel (Taxotere; Rhône-Poulenc Rorer, Collegeville, Pa), 75 mg/m² body surface area, was used in gynecological malignant neoplasms previously treated with chemotherapy. The intraperitoneal temperature is allowed to fluctuate from 41°C to 43°C, and the duration of the perfusion is 2 hours. To facilitate uniform temperature and drug distribution throughout the peritoneal cavity, vigorous agitation of the abdomen is performed continuously. The core temperature is kept below 38.5°C. After completion of the CHPPC, the abdomen is reopened, the canulae and probes are removed, and the excess fluid is dried from the abdominal cavity. The sump drain is left in place for postoperative drainage. The abdominal wall is closed in layers in the usual way.

Chemotherapeutic agents are usually administered systemically. In recent years, regional administration of chemotherapy has been attempted in an effort to achieve high levels of the cytotoxic agent locally without systemic toxic effects. Regional chemotherapy is an established treatment in limb sarcomas and melanomas and in secondary liver and lung neoplasms using intra-arterial infusion or isolated perfusion of the extremity or organ. The perfusion technique for peritoneal carcinomatosis has not been standardized.

Four decades ago, intraperitoneal chemotherapy began with the instillation of the drug into a small volume of dialysate. The distribution of the dialysate in the peritoneal cavity was poor, and the method was abandoned. To overcome the obstacle of incomplete sero-peritoneal exposure, larger volumes were introduced in the abdominal cavity for 1 to 2 hours. Since inadequate distribution of the drug to upper abdominal and small-bowel surfaces remained one of the most impor-

Figure 1. The closed perfusion system.
tant causal factors for recurrence of peritoneal carcinomatosis, other treatment strategies were developed.5

Recently, CHPPC has been introduced with the heated perfusate circulating continuously through the peritoneal cavity. Hyperthermia is often used because it has a direct cytotoxic effect and amplifies the activity of most cytotoxic drugs.6,7 The only limitation of the method is that it requires anesthetization, because intraperitoneal heat and chemotherapy are badly tolerated. Cytoreductive surgery always has to precede CHPPC during the same procedure, since the penetration depth of hyperthermic chemotherapy is estimated to be limited to 5 mm.8,9

Continuous peritoneal perfusion chemotherapy has certain advantages, such as the ability to wash out intraperitoneal free cancer cells, the combination with hyperthermia, direct exposure of the tumor to the drug, uniform distribution of the drug throughout the abdominal cavity, and the very high intraperitoneal drug concentration in relation to very low plasma levels.6,7 The latter is attributed to the peritoneal-plasma barrier and the first-passage clearance of many drugs by the liver. Depending on their molecular weight, their affinity for lipids, and first-passage effect by the liver, the plasma concentration gradient of the drugs in the peritoneal cavity may be as high as 1000, as is the case with paclitaxel.7 The disadvantages of the technique are the need for specialized personnel and apparatus as well as the prerequisite of an anesthetized patient to achieve maximal muscle relaxation and to tolerate the intraperitoneal heat and chemotherapy.

Continuous peritoneal perfusion can be performed using an open or a closed circuit.6,7 Most surgeons prefer the closed-circuit model described by Spratt et al10 in 1980, in which the perfusate circulates continuously. Their model is more economically efficient because of the lower drug level and lower heat loss.11-14 To optimize the exposure of the serosal surface of the abdominal organs and the parietal peritoneum to the perfusate and to achieve a better distribution of heat and drug, Fujimara et al11 introduced the concept of the “expanded peritoneal cavity” in an attempt to provide additional space for the peritoneal contents to float freely in the perfusate. They use an acrylic cylinder called a peritoneal cavity expander. The surgical wound is closed around the cylinder, and

Figure 2. Changes in hemodynamic variables and core temperature during hypothermia and subsequent intraperitoneal hyperthermia with artificial ascites during 23 continuous hyperthermic peritoneal perfusion chemotherapy procedures. Per Pr indicates peritoneal pressure; CVP, central venous pressure; TPA, pulmonary artery temperature; and PCWP, pulmonary capillary wedge pressure. All data are given as mean ± SD.
the abdominal cavity remains open through the cylinder. The intestine floats in the perfusate, and the surgeon’s hand stirs the perfusate to secure even distribution. In our proposed modification, satisfactory expansion of the peritoneal cavity is achieved by producing an artificial ascites with the abdominal cavity closed, in most cases infusing isotonic sodium chloride solution at approximately 3.5 L/m² body surface area. Since the total dose of the cytostatic drugs is calculated also per square meter of body surface area, the perfusate concentrations are expected to be nearly equal for all patients, to whom the same drug dose per square meter of body surface area is administered.

In comparison with the other techniques used, our modification is more efficient regarding heat loss; it prevents evaporation of the drug, decreases the risk for contamination, and maintains a tight surgical field. A significant leakage of perfusate at the base of the peritoneal cavity expander has been reported. On this point, this closed-circuit technique is safer for the theater personnel by minimizing their exposure to the drug. In addition, a recent animal study demonstrated that raised intra-abdominal pressure may increase drug penetration into tissues. Perfusion with an open abdominal cavity results in incomplete exposure of the intestine floating on the fluid surface and of the laparotomy wound to the perfusate. A high incidence of early wound recurrence has been reported after the use of the peritoneal cavity expander.

As in other situations, patients tolerated increased intra-abdominal pressure very well. In patients with cirrhosis, a volume of 7 to 9 L ascites with an intra-abdominal pressure of 16 to 20 mm Hg is common. In minimal invasive abdominal surgery, intra-abdominal pressure is raised to 14 mm Hg without any major adverse effects.

The hemodynamic data show that there are no significant adverse effects on the patient’s condition that cannot be handled (Figures 2 and 3). The cardiopressant effect of hypothermia during the period of extensive surgical maneuvering is significant, making the administration of vasoactive drugs mandatory in 14 of 23 cases. The stimulatory effect of the subsequent hyperthermia on the cardiovascular system usually diminished the need for these

Figure 3. Changes in hemodynamic variables and core temperature during hypothermia and subsequent intraperitoneal hyperthermia with artificial ascites during 23 continuous hyperthermic peritoneal perfusion chemotherapy procedures. SAP indicates systolic arterial pressure; DAP, diastolic arterial pressure; SPAP, systolic pulmonary arterial pressure; and DPAP, diastolic pulmonary arterial pressure. All data are given as mean ± SD.
drugs. The increase in pulmonary artery and central venous pressure could be attributed to the sympathetic effect of hyperthermia or to the increased intra-abdominal pressure transmitted to the thoracic cavity. Cardiac preload probably decreases response to the increased intra-abdominal pressure.\textsuperscript{18} It would therefore be prudent to observe these patients with extensive invasive monitoring during the whole procedure, because patients with marginal cardiovascular reserves might decompensate acutely.

One patient died within 1 month after the procedure, of intra-abdominal hemorrhage and leakage of a colorectal anastomosis, resulting in a mortality rate of 4% in our series. The mortality rate of our series is comparable with those reported by others, varying from 0% to 14%, regardless of the technique used.\textsuperscript{11,19,23} Major complications from different techniques have been reported in up to 44% of the cases.\textsuperscript{6,7,11,22,23} In our series, the remaining complications observed were minor and did not seem to be related to the expansion technique. The relatively high rate of wound complications may be attributed to the bad nutritional state of the patients, the systemic effect of the chemotherapeutic agent, and local exposure of the abdominal wound to hyperthermic chemotherapy. Transient renal insufficiency, observed in both cases in which higher doses (120 mg/m\textsuperscript{2} body surface area) of cisplatin had been used, was probably related to the resorption of this intraperitoneally administered nephrotoxic drug. This had been reason to decrease the dose again to 100 mg/m\textsuperscript{2}. The other complications were not related to increased drug doses. The leukopenia and thrombocytopenia were other chemotherapy-related complications, although the extensive blood loss during operation also contributes to the latter. The episodes of atrial fibrillation in 3 patients may be attributed to fluid disturbances in the early postoperative period after CHPPC.

We have strong reason to believe that our proposed modification of closed-circuit CHPPC is efficient, safe, and effective and should be tried by other centers using this treatment method. It remains to be proved in multicenter trials whether the theoretical advantages of the proposed technique will also lead to better long-term results.

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REFERENCES


The authors provide a modification in technique of hyperthermic peritoneal perfusion for peritoneal adenocarcinomatosis that builds on earlier studies. However, there are technical and cytokinetic limitations to their approach. From the technical standpoint, their perfusion system would not avoid streaming of flow. Like the authors, my approach would be to resect the primary cancer, omentum, and as much of the peritoneal implants as possible. Afterward, I would copiously irrigate the peritoneal cavity with 5% dextrose in water heated on last wash to 55°C and leave it in for only 3 to 5 minutes before removing. This temperature for short exposure is as thermolethal as the lower temperature used by the authors for longer periods. There is some evidence that the mucopolysaccharides forming the viscous ascites in pseudomyxoma peritonei are miscible in 5% dextrose in water. Also, 5% dextrose in water has an osmolytic effect on cells. The solution is not removed, but will be absorbed into the circulation. From this point on, my chemotherapy technique, developed with Thomas Woodcock, MD (unpublished data, 1998) is influenced by the fact that many cases of peritoneal carcinomatosis are composed of cancer cells with very low proliferative indexes. With antiprofibrinolytic drugs only, cells that are in cycle will be affected by the drugs. This requires a more protracted course of chemotherapy, which is obtained by inserting a titanium peritoneal port (PORT-A-CATH [catalog No. 21-2000]; Pharmacia Deltech Inc, St Paul, Minn) before abdominal closure. Drugs are administered via the PORT-A-CATH at weekly intervals for 6 weeks, followed by a 2-week rest. The drugs are diluted in 2000 mL 5% dextrose in water. The solution is not removed but will be absorbed. This volume is necessary for diffusion to occur throughout the peritoneal cavity. The course continues for 1 year. In the case of bowel cancer, the weekly course consists of 750 mg of fluorouracil and 1000 mg of leucovorin calcium. This is very well tolerated. Lorazepam (Ativan) can be given before each treatment for the prevention of nausea.

Technically, the PORT-A-CATH is easier to manage and has less risk for complications than the intravenous route. If I were to design a clinical trial for the adjunctive therapy of bowel cancer, I would use this technique with some modification of the drugs as dictated by the cancer being treated. Many aspects of peritoneal carcinomatosis were reviewed in a monograph published in 1986. These comments update that monograph.

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