Intraperitoneal Heated Chemotherapy Affects Healing of Experimental Colonic Anastomosis: An Animal Study

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Background: The peritoneal spread of cancer is a well-known entity carrying a dismal prognosis. A new therapeutic approach is the combination of cytoreduction with heated intraperitoneal chemotherapy (HIPC). The risk of an intra-abdominal anastomosis in the presence of such chemotherapy is recognized clinically but the experimental data on the subject are lacking. The aim of this study is to examine the influence of chemotherapy and hyperthermia on the healing of colonic anastomosis.

Materials and Methods: Colonic anastomosis were performed in four groups of male Wistar rats: (1) control (operation only), (2) HIPC with saline, (3) with mitomycin C (MMC), and (4) with cisplatinum. HIPC was performed using a closed circulation system at 40°C over 20 min. Anastomotic strength was tested on day 4, 7, 10, and 21.

Results: The bursting pressure of anastomoses in rats treated by HIPC was significantly lower than in controls. On day 4, it was 54.8 mm Hg, 38 mm Hg, 18 mm Hg, and 14.8 mm Hg in groups 1–4, respectively, while on day 7 it was 170 mm Hg, 188 mm Hg, 83 mm Hg, and 19 mm Hg, respectively (P < 0.01). The difference decreased on day 10 and almost vanished on day 21. HIPC with cisplatinum had the worst effect on anastomotic healing during the early postoperative period.

Conclusions: Cytoreduction and HIPC are gaining popularity. However, the use of heated chemotherapy has a detrimental effect on the strength of colonic anastomosis, especially during the early postoperative period (until day 10). This may cause anastomotic failure and postoperative morbidity. Therefore, careful selection and avoidance of unnecessary anastomoses are mandatory.


KEY WORDS: peritoneal carcinomatosis; hyperthermia; cis-platinum; mitomycin-C; intraperitoneal chemotherapy

INTRODUCTION

Intraperitoneal cancer spread (peritoneal carcinomatosis) is a uniformly lethal, terminal stage of abdominal malignancies. There is no curative treatment, and few palliative treatment modalities are available. Most patients with peritoneal carcinomatosis die within 6 months [1–5].

Recently, a new approach involving aggressive cytoreductive surgery and heated intraperitoneal chemotherapy (HIPC) has been designed [2,6,7]. The new treatment has gained popularity among surgical oncologists since it has a good palliative effect and even offers the possibility of long-term survival for some patients with abdominal carcinomatosis [2,4,6,8–12].

The cornerstone of the new approach is resection of neoplastic tissue, with or without peritonectomy, aimed at...
reducing tumor load to the lowest possible level. Heated (41–42°C) high dose chemotherapy is then administered during the operative procedure and the early postoperative period in order to eliminate minimal residual disease: the most commonly used drugs being mitomycin C (MMC) or cisplatinum [10,18]. This is an aggressive surgical procedure involving major bowel resection and anastomoses.

The procedure is not devoid of complications, and significant morbidity as high as 35% and mortality of at least 5% have been reported [12–22]. The combination of a major, aggressive surgical procedure including bowel resection and anastomosis, together with the detrimental influence of cytotoxic chemotherapeutic agents and high temperature on anastomotic healing, may be a reason for this morbidity and mortality, one of the common complications being anastomotic leak [19,21–24].

To the best of our knowledge, the influence of intraperitoneal chemotherapy and high temperature on anastomotic breaking strength and healing has not been studied experimentally. The present study addresses the question in an animal model.

MATERIALS AND METHODS

Male Wistar rats of median weight 440 g (range 380–490 g) were used. Rats were housed in a metal box container, with a maximum of three rats per cage. Standard laboratory pellet formula and tap water were provided. All experimental procedures were performed according to our institution’s guidelines for the care and use of laboratory animals and had received the approval of our Ethics Committee.

Surgical Model

The animals were anesthetized by an intraperitoneal injection of ketamine. Prior to surgery, a single dose of second generation cefalosporine antibiotics was given by intramuscular injection.

A midline laparotomy was performed using the standard operative technique. The cecum was found and a transverse incision of the colonic wall performed just 2 cm above the ileo-cecal joint. At least 70–80% of the colonic wall circumference was incised and then anastomosed using 5/0 silk interrupted sutures [25]. The animal was then prepared for intraperitoneal chemotherapy. Two large bore (14 G) intravenous canulas were introduced into the abdominal cavity through the flanks (Fig. 1) and connected to a closed perfusion system (Watson-Marlow, Falmouth, Cornwall, UK) comprising two pumps and a reservoir containing saline heated to 40°C, which served as the perfusate.

HIPC using 200 cc of perfusate without a chemotherapeutic agent in one group, and MMC or cisplatinum, in two groups minutes was performed over 20 min. Upon completion of the perfusion, the abdominal muscle layer and skin incision were closed separately with running sutures (4/0 silk). In the control group, colonic anastomosis without perfusion was performed in the same manner.

Study Design

A total of 96 rats were randomized into four groups: (1) control, (2) heated saline perfusion, (3) HIPC with MMC, 0.02 mg/ml of perfusate, and (4) cisplatinum, 0.1 mg/ml of perfusate. The total dose of MMC was 4 mg and of cisplatinum 20 mg. Following anastomosis and HIPC, animals were killed by ether inhalation on day 4, 7, 10, or 21. The abdomen was opened and the anastomosis found and carefully dissected. The macroscopic appearance of the anastomotic site (abscesses, fibrin layer, adhesions) was recorded. After complete dissection, the segment with the anastomosis (margins of 2 cm on each side) was removed.

The distal end of the examined colon segment was tied. A cannula was inserted into the intestinal lumen via the proximal end to a distance of 1 cm and the intestine was tied over it. Proximally, the cannula was connected to two channels: to an infusion pump at a rate of 2 ml/min of normal saline and to a pressure recorder (Neonatal Monitor 744, Mennen Medical, Inc., NJ) via a pressure transducer (Fig. 2). The pressure at which leakage/rupture of the
anastomotic line occurred was recorded as the bursting pressure (BP). Data were expressed as mean ± SD [25].

**Statistical Analysis**

Results are given as median (range). Statistical significance between mean values at each time point in each group was determined by analysis of variance. The SAS system was used to analyze and compare results.

**RESULTS**

All animals survived the operation. Four days after the procedure, a significant inflammatory reaction (fibrin layer, edema of bowel wall) was noted in all groups. There were two macroscopically anastomotic failures in each of the HIPC groups, one failure in the saline group and one in the control group, all of which were excluded from the analysis. Mean bursting pressure was 54.8 mm Hg ± 8.8 in the control group, 38 mm Hg ± 12.4 in the heated saline perfusion group, 18 mm Hg ± 1.6 in the MMC group, and 14.8 mm Hg ± 2.4 in the cisplatinum group. The bursting pressure in the experimental groups was significantly (P < 0.001) lower than in the controls.

On the 7th postoperative day, mean bursting pressure was 185.3 mm Hg ± 12.8 in the controls and 188 mm Hg ± 26.3 in the saline perfused group, but in the chemotherapy groups it was significantly lower; 83 mm Hg ± 12.6 in the mitomicin C and even lower, 19 mmHg ± 4, in the cisplatinum group (P = NS).

It should be noted that in the chemotherapy groups, the mean bursting pressure was significantly lower than in controls at all times until day 21 (Fig. 3). There was also a difference between the chemoperfusion groups as well. The bursting pressure of anastomosis in the cisplatinum group was lower than that of the MMC group during the first week post-surgery. This difference decreased thereafter but the statistical difference (P < 0.001) was preserved until day 21.

**DISCUSSION**

Peritoneal carcinomatosis is a grave sign of advanced cancer. The probability of cure is extremely low, and patients are usually considered non-treatable by surgery. Recent publications, however, suggest that in selected patients with peritoneal, but not visceral, spread of cancer, and in whom resection of all or most macroscopic disease is feasible and reasonable, one can perform cytoreduction. The procedure will inevitably leave tumor cells behind (minimal residual disease), or even tumor implants of less than 2–3 mm. These patients should then be eligible for HIPC aimed at eradicating residual disease and taking advantage of the synergism between chemotherapeutic drugs and hyperthermia similar to other systems of organ perfusion such as isolated limb or isolated hepatic perfusion.

Cytoreduction has been reported for a variety of cancers; ovary [6], colorectal [1,8,11,18], gastric [2,4,7,14], sarcoma [12], and pseudomyxoma [10], with promising results. The procedure is accompanied by

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**MEASUREMENT OF BURSTING PRESSURE OF COLONIC ANASTOMOSIS**

![Fig. 2. Schematic illustration of method of recording anastomotic bursting pressure.](image)

**ANASTOMOTIC HEALING IN EXPERIMENT**

![Fig. 3. Graph showing changes in anastomotic bursting pressure according to postoperative day in all groups.](image)
morbidity and mortality associated with anastomotic complications such as leakage, abscess, and fistula formation. Whether this is due to patient factors such as performance status, previous treatments, myelosuppression, impaired kidney function, etc., or due to a detrimental effect of HIPC on anastomotic healing is unknown.

A surgical model of anastomosis of the colon with HIPC was developed to test the effect of hyperthermia and chemotherapy on anastomotic healing. The end point of the present study was bursting pressure; the pressure at which leakage/rupture of the anastomotic line occurred after filling the bowel segment with saline at increased pressures. For control, we used a group of animals undergoing anastomosis alone, without HIPC.

The natural course of anastomotic healing is characterized by a slow increase in bursting strength during the first four postoperative days and a quick rise thereafter. Burst pressure was low for a week in all treatment groups including the saline alone group, suggesting a role for the hyperthermia. Chemotherapeutic agents, however, had a profound effect on the early bursting pressure and delayed increase in anastomotic strength. Furthermore, there was a difference in anastomotic strength depending on the type of chemotherapeutic agent used. Although cisplatinum had a worse effect than MMC on anastomotic strength during the first ten postoperative days, thereafter there was an increase in anastomotic strength in the cisplatinum group compared to the MMC group. In both groups, anastomotic bursting pressure was lower than in the saline and control groups at all time points until day 21.

Our explanation for this difference in anastomotic strength between chemotherapy and control groups is a detrimental effect of chemotherapeutic agents on wound healing. It is difficult to say whether the decrease in anastomotic burst strength compared to hyperthermia alone is due to systemic or local factors. Bozdag et al. [26] in an experimental study have demonstrated detrimental effect of a chemotherapeutic (5-Fluorouracil) on anastomotic healing but also could not determine the exact mechanism of this effect. A study by Jansen et al. [27] using carbon absorbed Mitomycin-C suggested a role for local direct effect.

This may have great significance in understanding morbidity after cytoreduction and intraperitoneal chemotherapy, especially during the early postoperative period.

We suggest that HIPC has a detrimental effect on the healing and strength of intestinal anastomoses, which may explain the relatively high morbidity rates following this procedure. This influence is especially high during the first postoperative week, which may dictate the use of additional monitoring and therapeutic measures. It may also be necessary to decrease the number of anastomoses performed during one procedure or even to delay an anastomosis to a second stage procedure upon completion of the chemotherapy in selected cases. Taking the above into consideration that could assist in patient and procedure selection. With due caution and attention to surgical details, cytoreduction ± HIPC is a viable option.

REFERENCES