

The effects of intraperitoneal chemotherapeutic agents on adhesion formation

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Summary

Purpose: Intra-abdominal adhesions are a major complication of healing. Furthermore these adhesions may cause morbidity and sometimes mortality for patients, and also are a financial burden to the health system. **Materials and Methods:** Cecum abrasion was performed in all rats and solutions containing saline to group 1, 5-fluorouracil to group 2, cisplatin to group 3, paclitaxel to the group 4, and mitomycin-C were administered into the abdomen of the groups, respectively. The intra-abdominal adhesions were scored after the macroscopic evaluation. **Results:** Among the chemotherapeutic drugs, paclitaxel significantly increases occurring of intra-abdominal adhesions in comparison with the control group and the other drugs according to the evaluation of scoring and statistical studies. **Conclusion:** It is suggested to use the drugs which have a proven anti-adhesion feature or barriers to the patients who are going to be applied intraperitoneal chemotherapy with paclitaxel.

Key words: Intra-abdominal adhesions; Intraperitoneal chemotherapy; Cytoreductive surgery.

Introduction

Adhesions formed after abdominal operations continue to be a problem for surgeons. Intra-abdominal adhesions still to date affect the patient's quality of life while increasing morbidity, mortality, and costs [1]. It has been observed that adhesions formed in the patients who have intra-abdominal operations range between 64-97%, and this ratio has been found to be higher after laparotomy procedures compared to laparoscopic procedures [2, 3].

In recent years, the treatment methods like cytoreductive surgery and intraperitoneal chemotherapy have been used. Previous to this, the prognosis of patients with peritoneal carcinomatosis inevitably resulted in death because of intestinal obstruction [4-7]. Average survival in these patients was about six to nine months despite the treatments and systemic chemotherapy was not effective enough. Moreover, intraperitoneal chemotherapy did not influence the nodules with large diameters [8]. Today, five-year survival can be achieved by using a complete cytoreduction, perioperative intraperitoneal hyperthermic perfusion chemotherapy (HIPEC), and early postoperative intraperitoneal chemotherapy (EPIC) which are made by proper patient selection [9].

In the present clinic, during relaparotomy that the authors have practiced for ileostomy-colostomy closure, for intervention to recurrence, for the second or third HIPEC or for any other reason, have observed that there are prevalent and severe adhesions among the patients with colorectal, ovary, and stomach cancers and among the patients with primary

peritoneal mesothelioma who had chemotherapy administration in the post-cytoreductive surgery.

In this study, the aim was to investigate the potential impacts of intraperitoneal chemotherapeutic drugs applied following the cytoreductive surgical procedure called 5-fluorouracil, cisplatin, paclitaxel, and mitomycin-c on intra-abdominal adhesion formation.

Materials and Methods

Before the study, the approval of the Animal Experimentation Ethics Committee of Cumhuriyet University had been received.

In this study, 35 Wistar-Albino male rats, weighing between 200-250 grams (275 grams on average), were used. Rats were fed with standard food and tap water, and kept at ambient temperature from 21 to 23 degrees during the experiment. Laboratory animals were randomly divided into five groups with seven per each.

The rats were separated into groups of seven and after opening the abdomen with two-cm median laparotomy, the same surgeon removed the caeca and the front wall of the cecum was traumatized by using a number 15 scalpel. Sterile powder-free gloves and surgical instruments were used during the process. While performing this process, only serosal injury was created and the traumatized area was carefully handled in order to avoid perforation and excessive bleeding. The following procedures were respectively applied to the groups: Group 1: laparotomy + cecum abrasion + two ml 0.9% NaCl (normal saline); Group 2: laparotomy + cecum abrasion + two ml solution of 5-fluorouracil (600 mg/m²); Group 3: laparotomy + cecum abrasion + two ml solution of cisplatin (100 mg/m²); Group 4: laparotomy + cecum abrasion + two ml solution of paclitaxel (175 mg/m²); Group 5: laparotomy + cecum abrasion + two ml solution of mitomycin-c (30 mg/m²)

In the present study, early postoperative intraperitoneal chemotherapy (EPIC) rat model was established in order to elim-

Table 1. — Scoring of intra-abdominal adhesions, according to Nair scale.

Grade	Description of adhesion bands
0	There is no adhesion
1	Availability of only one adhesion band between organs or between the organ and abdominal wall
2	Availability of two bands between organs or between the organ and abdominal wall
3	Availability of more than two bands between organs or between the organ and abdominal wall or formation of mass by all intestines without adhesion to the abdominal wall
4	Adhesion of an organ to the abdominal wall without considering the number and prevalence of adhesion bands

Table 2. — Scoring of intra-abdominal adhesions, according to severity of the adhesion.

Grade	Description of adhesion bands
0	There is no adhesion
1	Thin and vascular adhesions
2	Thick and vascular adhesions
3	Adhesions in the form of organs and tissues sticking together

inate factors such as heat, drain, anastomosis, dissection width, and in order to see only the effects of the chemotherapeutics given intraperitoneal and ensure standardization. Looking at the literature, the authors found that the number of treatment administrations varied according to the primary type of cancer and the type of drug used. In terms of standardization of the present study, the authors applied a single cure intraperitoneal chemotherapy to all subjects under the same conditions. Drug doses were determined and applied in accordance with the literature: for 5-fluorouracil 600 mg/m², for cisplatin 100 mg/m², for paclitaxel 175 mg/m², and for mitomycin-c 30 mg/m² [10].

Abdomen was closed in two layers. While the abdominal wall was closed with 3/0 absorbable materials with continuous suture, the skin was closed 3/0 non-absorbable sutures, one by one [11].

Mortality and morbidity was not observed in any rat for 14 days. The rats were sacrificed by using high doses of sodium pentobarbital at the end of 14th day (20 mg/kg). Previous abdominal midline incision was checked and by paying attention not to place on the upper part of previous laparotomy area, the abdomen was

Table 3. — Scoring of intra-abdominal adhesions, according to prevalence of the area kept.

Grade	Description of adhesion bands
0	There is no adhesion
1	If the adhesion covers less than 25% of the traumatized area
2	If the adhesion covers 26-50% of the traumatized area
3	If the adhesion covers more 50% of the traumatized area

Table 4. — Statistical results of scoring of intra-abdominal adhesions, according to Nair classification.

Groups:	N	Mean	SD	Median	
Control (SF)	7	1.14	0.69	1	$p = 0.002^*$
5-Fluorouracil	7	0.29	0.76	0	
Cisplatin	7	0.71	0.76	1	
Paclitaxel	7	2.57	0.98	3	
Mitomycin-c	7	0.57	0.53	1	

grafted with a “U” shaped incision, and the peritoneal cavity and cecum were evaluated. Intra-abdominal adhesions were evaluated with the defined scores according to the scale (Table 1) described macroscopically by Nair [12] in the adhesion scoring system of Adhesion Scoring Group (ASG), according to the severity [13, 14] (Table 2), and the prevalence of adhesions [15] (Table 3).

Statistical method

Statistical data of the present study were evaluated with Kruskal-Wallis test, Mann-Whitney U tests in SPSS program (ver.14.0). The present data were specified in the tables as the number of subjects, \pm standard deviation, median, and error percentage was considered as 0.05.

Results

Adhesions were observed to various degrees in all study groups. When adhesion grades were compared in the scoring of intra-abdominal adhesions, a significant difference was found between the groups ($p < 0.05$); according to Nair classification (Table 4). When the adhesion values of groups were compared in pairs, a significant difference was

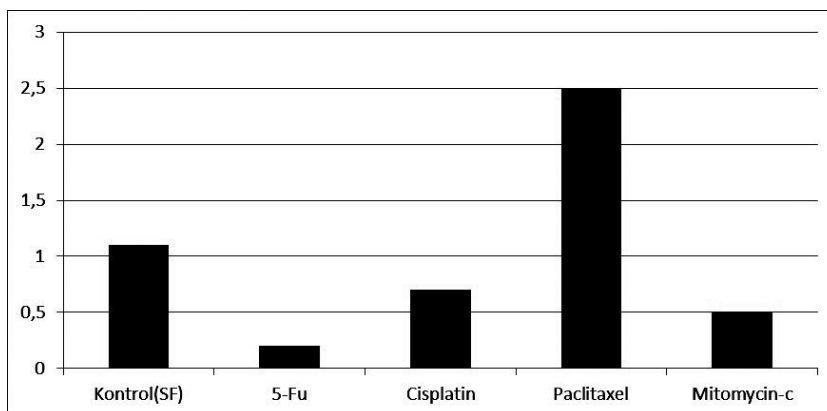


Figure 1. — The distribution of the averages of intra-abdominal adhesions, according to Nair classification.

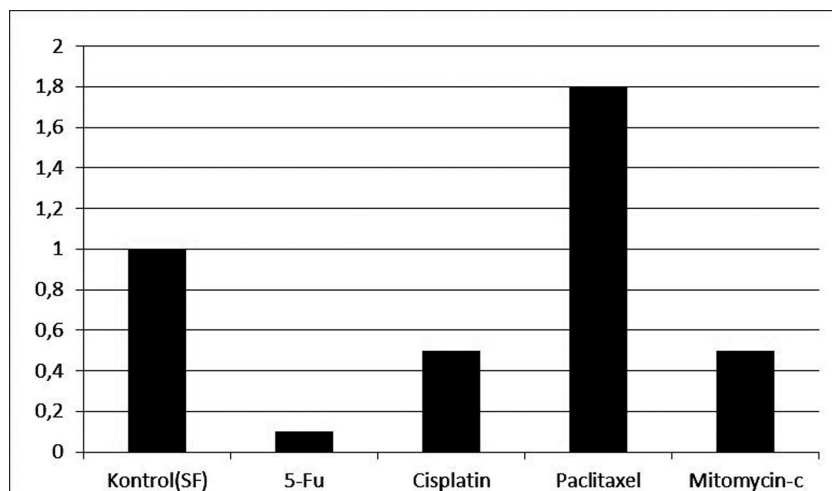


Figure 2. — The distribution of averages of intra-abdominal adhesions regarding the groups, according to severity of the area involved.

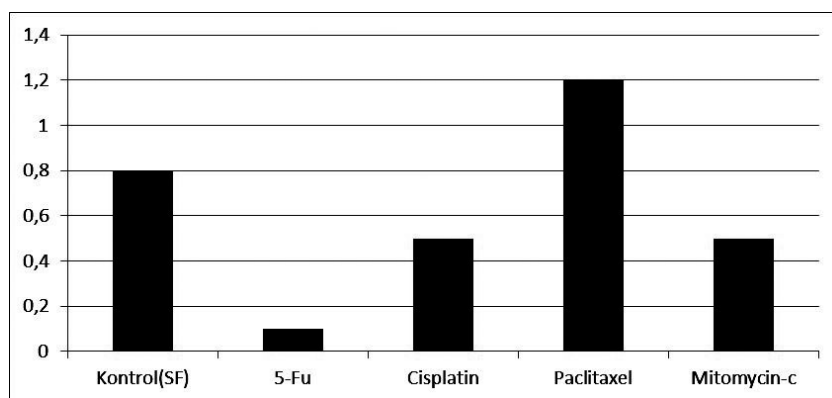


Figure 3. — The distribution of averages between groups in the scoring of intra-abdominal adhesions, according to the prevalence of adhesions.

Table 5. — Statistical results of scoring of intra-abdominal adhesions, according to severity of the area involved.

Groups:	N	Mean	SD	Median	
Control (SF)	7	1.00	0.58	1	$p = 0.001^*$
5-Fluorouracil	7	0.14	0.38	0	
Cisplatin	7	0.57	0.53	1	
Paclitaxel	7	1.86	0.69	2	
Mitomycin-c	7	0.57	0.53	1	

Table 6. — Statistical results of scoring of intra-abdominal adhesions, according to the prevalence of adhesions.

Groups	N	Mean	SD	Median	
Control (SF)	7	0.86	0.38	1	$p = 0.010$
5-Fluorouracil	7	0.14	0.38	0	
Cisplatin	7	0.57	0.53	1	
Paclitaxel	7	1.29	0.76	1	
Mitomycin-c	7	0.57	0.53	1	

observed between the control group and the paclitaxel group, 5-FU group and the paclitaxel group, the cisplatin group and the paclitaxel group, mitomycin group and paclitaxel group ($p < 0.05$), the difference among the other groups was found to be insignificant (Figure 1).

When adhesion grades were compared in the scoring of intra-abdominal adhesions, a significant difference ($p < 0.05$) between the groups was found, according to severity of the area involved (Table 5). When the adhesion values of groups were compared in pairs, a significant difference was found between the control group and the paclitaxel group, 5-FU group and the paclitaxel group, the cisplatin group and the paclitaxel group, mitomycin group and paclitaxel

group ($p < 0.05$), the difference among the other groups was found to be insignificant (Figure 2).

When adhesion grades were compared in the scoring of intra-abdominal adhesions, a significant difference was found between the groups ($p < 0.05$), according to prevalence of the adhesion (Table 6). When the adhesion values of groups were compared in pairs, a significant difference was found between the control group and the 5-FU group, 5-FU group and the paclitaxel group, the cisplatin group and the paclitaxel group, mitomycin group and paclitaxel group ($p < 0.05$), the difference between the other groups was found to be insignificant (Figure 3).

Discussion

Intra-abdominal adhesion is an important source of problem for the patient, surgeon, and the community. Since the beginning of surgical practice, all surgeons have been in the search of the perfect and faultless surgery method. Despite the significant improvements in the surgical techniques, adhesion formation has been continuing to be one of the most important problems of surgery. While the incidence of intraperitoneal adhesions is between 67-93% in postoperative general surgery, incidence of adhesions after gynecologic surgery can be seen in up to 97% of cases [16, 17]. As the number of operations that a patient undergoes increases, the ratio increases as well; 3% of operations performed in abdominal surgery is due to the formation of adhesions [16].

Five-year survival can be achieved, which can be accepted as 'cure' for some patients, by using a complete cytoreduction (surgical resection) and intraperitoneal chemotherapy (perioperative intraperitoneal hyperthermic intraperitoneal chemotherapy or postoperative chemotherapy) [18-20]. It has been shown in pharmacokinetic studies that agents such as mitomycin C, 5-fluorouracil, doxorubicin, cisplatin, paclitaxel, and gemcitabine can be used more effectively intraperitoneally than intravenously for the treatment of peritoneal carcinomatosis and sarcomatosis [21, 22]. In the present clinic, the authors also applied intraperitoneal chemotherapy post-cytoreductive surgery among patients with colorectal, ovarian, primary fallopian tube, and gastric cancers, and among the patients with primary peritoneal mesothelioma. During relaparotomy that the authors practiced for ileostomy-colostomy closure, intervention to recurrence, second HIPEC or for any other reason, they have observed prevalent and severe adhesions in these patients. They have also encountered very dense adhesions during relaparotomy especially among the patients undergoing surgery and in which intraperitoneal chemotherapy by paclitaxel was applied due to epithelial ovarian cancer and peritoneal mesothelioma.

In the study carried out by Demirtürk *et al.*, two most commonly used scoring systems were compared and a significant difference was found between them [23]. Although it is not statistically significant, the difference between the observers in the same scoring system is thought to affect the results. The experience of the researcher with the scoring system has also an influence on the results [23]. In the present study, three different adhesion scoring systems were used by a single surgeon and the intra-abdominal adhesions were evaluated with those scoring system. Thus, the authors aimed to increase the reliability of the test.

Paclitaxel, mitomycin-C, cisplatin, and 5-FU are effective drugs which have been commonly used in intraperitoneal chemotherapy. Therefore, they were preferred in this study [24, 25]. Crystalloids act by flotation. Giving 300 ml to 500 ml of crystalloid liquid to peritoneal cavity in the postsurgical procedure, "floatation" of abdominal and

pelvic organs was listed as a method in the prevention of intra-abdominal adhesions [26].

A significant difference was found between the drugs used, and paclitaxel was shown to be the most effective agent among these drugs on the formation of adhesion, according to all three of these adhesions assessment methods used in this study.

Conclusion

As a result, paclitaxel, which was applied as intraperitoneal, was observed to increase the occurrence of intra-abdominal adhesion much more significantly, compared to the control group and the other chemotherapeutic agents.

Intraperitoneal chemotherapy practiced during and post-cytoreductive surgery in advanced stage of abdominal cancers is a very tiring and painful treatment process that requires patience and morale for the patient, caregivers, and the treatment team. During or after this process, side effects such as abdominal pain, nausea, vomiting, and intestinal obstruction may occur among the patients due to adhesions and this will cause suffering, concern, and fear for the patients and relatives who struggle against cancer or even think that they have defeated cancer, and it will affect certainly the entire treatment process.

As a result of the present authors' own clinical experiments and the study they have performed, they have observed that there is dense adhesion in the patients who undergo surgery due to epithelial ovarian cancer and peritoneal mesothelioma and have HIPEC with paclitaxel. It has to be taken into account that there will be dense adhesions in the patients to whom this treatment is going to be applied.

In addition, these patients may need ileostomy-colostomy. Relaparotomy may be needed for ileostomy-colostomy closure, for resection of recurrence during follow-up, or for repeated intraperitoneal chemotherapy. Therefore, in order to reduce the risks of chronic abdominal pain, intestinal obstruction attacks depending on the abdominal adhesions, and to reduce risk of formation of complication depending on adhesion during relaparotomy, the present authors suggest that using agents or barriers which have prophylactically preventing adhesion characteristic which have been proven with studies will be useful.

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