The effect of chemotherapy with 5-fluorouracil, bleomycin and cisplatin in the healing of colonic anastomoses in rats

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The effect of chemotherapy with 5-fluorouracil, bleomycin and cisplatin in the healing of colonic anastomoses in rats

PURPOSE: *Chemotherapeutic factors are known to affect healing on the postoperative patient. The aim of the present experimental study was to evaluate the effect of intraperitoneal infusion of 5-fluorouracil, bleomycin and cisplatin on the healing of colonic anastomoses in rats.*
METHODS: *Forty Albino-Wistar male rats were randomly divided into two groups, a control and a chemotherapy (CT) group. In both, an end-to-end colonic anastomosis was performed. collagen, In the control group, 2cc saline was administered intraperitoneally during the operation and daily postoperatively until the sacrifice. In the CT group, rats were administered a solution of 5-fluorouracil (20mg/kg b.w.), bleomycin (4mg/kg b.w.) and cisplatin (0.7 mg/kg b.w.) in an amount of 2cc intraperitoneal intraoperatively and afterwards daily postoperatively until the seventh postoperative day when they were sacrificed. At sacrifice, adhesion presence was calculated and the anastomoses were resected and macroscopically examined. Bursting pressures were calculated and histological features were graded. Hydroxyproline concentrations were evaluated.*
RESULTS: *No deaths or wound infections were observed until sacrifice. Bodyweight was significantly decreased in the CT group ($p=0.005$). Bursting pressures ($p=0.001$) were significantly lower in the chemotherapy group, whereas adhesions were significantly increased ($p=0.001$). Hydroxyproline concentrations were not significantly different ($p=0.401$). All histological parameters appeared significantly decreased in the CT group: inflammation ($p<0.008$), neoangiogenesis ($p<0.001$), and fibroblast activity ($p=0.001$) and collagen deposition ($p<0.001$).*
CONCLUSION: *The use of chemotherapeutic agents had negative effects on the healing process of colonic anastomosis in rats. The decreased inflammatory response depicts in more frequent anastomotic dehiscence, ruptures and bodyweight loss postoperatively.*

KEY WORDS: Adhesion, Bursting pressure, Collagen, Hydroxyproline, Inflammation, Neoangiogenesis

Introduction

Colon cancer is the third cause of death due to neoplastic diseases worldwide. Up to date, tumor resection of the affected part of the intestinal tract remains the management of choice in colon cancer. The reestablishment of continuity of the gastrointestinal tract requires the creation of a colonic [1,2]. Anastomotic healing plays a major role in the success of the operative outcome and in the fast recovery of the patient, since it is vital for the restoration of proper nutrition.
As any tissue of the human body, healing is a complex procedure consisting of 3 phases; inflammation phase, productive phase and anaplastic phase. Any discrepancy in these phases will cause a deficit in the proper healing of the anastomosis. Healing may be affected by var-

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ious factors, local or systemic, such as operative technique, sufficient oxygenation of the tissues, infections, patients' age, comorbidities, medication [3-63–6]. Anastomotic dehiscence is a major factor in total morbidity and mortality in patients after colon surgery. The leak of intestinal content into the peritoneal cavity can cause severe sepsis (peritonitis) and inevitably death [7]. The dehiscence of the anastomosis, which is the mechanical cause of leak, usually is presented the fifth to seventh postoperative day due to defective healing of it. Ruptures are more frequent in rectal than colonic anastomosis [8,9].

Adjuvant therapy to colon cancer resection is the administration of antineoplastic drugs with 5-fluorouracil, bleomycin and cisplatin being among the most commonly administered drugs in the management of colon cancer. These drugs are proven to decrease the frequency of cancer recurrence and mortality rates in patients administered as adjuvant therapy [10,11]. All three have been examined in intraperitoneal administration intraoperatively and have statistically significantly decreased local neoplasm recurrence, without the full spectrum of side effects after their systematic administration [12-21]. Nevertheless, antineoplastic drugs remain immunosuppressant drugs, meaning that they interfere with normal processes such as tissue healing [19,22-24].

Additionally, the immediate intraperitoneal administration of chemotherapeutic drugs that slow down the ability of fibroblasts to produce collagen has a negative impact in the healing of colonic anastomosis thus increasing the bursting pressure [19,20,23,25].

The aim of the current experimental study is to evaluate the level of effects of 5-fluorouracil, bleomycin and cisplatin in the healing of colonic anastomoses in rats. The healing of colonic anastomoses was clinically and laboratory evaluated by the following parameters; macroscopic examination, bursting pressure, histological assessment, and biochemical assessment.

Materials and Methods

Laboratory Animals

Forty male Wistar rats (average weight 200–300g) were used in the present study. The research protocol was approved by the Ethical Committee of the Department of Veterinary Services of the Prefecture of Thessaloniki (SN:13/10767/15-9-2003).

Laboratory animal care was strictly taken into consideration during the study. The rats were kept 7-10 days before the experiment in individual housing, unrestricted access to standard diet and water and on a 12-hour light cycle. Minimal pain and discomfort of rats was of high essence. None preoperative antibiotics were given. The same conditions existed also during the experiment.

Experimental Groups, Anesthesia and Operative Technique

Rats were randomly assigned to two groups of 20 animals. In the Control group, 2cc saline was administered intraperitoneally during the operation and daily postoperatively until the sacrifice. In the Chemotherapy (CT) group, rats were administered a solution of 5-fluorouracil (20mg/kg b.w.), bleomycin (4mg/kg b.w.) and cisplatin (0.7mg/kg b.w.) in an amount of 2cc intraperitoneal intraoperatively and afterwards daily postoperatively until the sixth postoperative day. For substances' administration, the rats were subjected to light sedation with ether. After satisfactory anesthetization for the administration of the substances by injection, the rats were repositioned in their cages. The initial and final weights of the rats were measured. The anastomosis was performed under general anesthesia. First, the animals were placed in a room with ether for a few seconds, and then thiopental solution was administered intraperitoneally at a dose of 50mg/kg of bodyweight. Total duration of the anesthesia was 50-60 minutes. Afterwards, abdominal hair was shaved, and 10% povidone iodine solution was used for proper antisepsis. Then, the rat was placed and immobilized on a disinfected surgical table, and a sterile surgical field was used to margin the surgical site. Through a 3 cm midline incision, the colon was recognized and at 10 cm distance of the ileocecal valve, on the transverse colon, 1 cm of colon, was excised. Afterwards, an end-to-end colonic anastomosis was created using a single layer of eight interrupted extramucosal 6-0 polypropylene sutures. Then, the peritoneal cavity was washed with saline (NaCl 0.9%), and the abdominal wall was closed with three or four silk sutures 3/0. No antibiotics were administered to animals, and the net surgical time ranged from 15 to 25 minutes.

Macroscopic Examination

The study animals were sacrificed on the seventh postoperative day. After anaesthesia, they were euthanized by intracardiac administration of KCL 10%. The anastomoses were examined macroscopically for the following parameters: integrity of the anastomosis, existence of abscess or peritonitis and adhesion formation. The evaluation of adhesion formation was performed according to the scale of van der Hamm et al. [26]. This scale ranges from 0 to 3 as follows; (0) no adhesions; (1) minimal adhesions; (2) moderate adhesions, *i.e.*, between the omentum and the anastomotic site; and (3) severe and extensive adhesions, including abscess formation.

Bursting Pressure

Ex vivo measurement of bursting pressure includes the

removal of the anastomosis along with a 5 cm segment of the colon in total *en bloc* with the formed adhesions. A manometer with the ability of continuous measurement of pressure was attached to a catheter securely placed in the distal end of the specimen, whereas the proximal end was tightly connected to a pump which provided a continuous flow of physiological saline at a rate of 1 mL/min. The bursting pressure was defined as the pressure at which leakage of saline or gross rupture was noted and was recorded in mmHg. The site of leakage during the bursting pressure measurement was also recorded, since rupture occurred at the anastomotic site or far from it.

Histological Assessment

After the bursting pressure measurement, the colon' segment was placed in 4% formaldehyde solution for histopathological examination. The histological sections were 3 μm thick and stained with hematoxylin and eosin. The Ehrlich and Hunt numerical scale as modified by Phillips *et al.* was used to histologically grade the microscopic findings [27]. The evaluated parameters were inflammatory cell infiltration (white blood cell count), angiogenesis, fibroblast activity and collagen deposition. Each studied parameter was evaluated individually using a numerical scale as follows: (0) no evidence, (1) occasional evidence, (2) light scattering, (3) abundant evidence and (4) confluent fibers or cells.

Hydroxyproline

In order to quantify the amount of collagen in the anastomotic area the total amount of hydroxyproline was measured. A segment of the anastomosis was freezed at –20 °C and after drying for 24 hours it was weighted on a high-accuracy scale. Then, it was placed in 30 μL of concentrated solution of sodium hydroxide (NaOH) of 8N and right afterwards T-chloramine 0.056N. The purpose of this was the extraction of the collagen from the tissue and conversion to solution form 500 μL of 1M Ehrlich reagent were added, and the solution was incubated. After this procedure, the solution was placed on a spectrophotometer, and the absorption was calculated at 550nm. With the help of an absorption curve and a mathematical formula, a calculation of hydroxyproline was performed.

Statistical Analysis Statistical Analysis

The extracted data were summarized using statistical descriptive indices of central tendency and dispersion. Data appear as mean value +/- standard deviation or median and range, whenever more appropriate. The data were evaluated depending on presentation of normal distribution or not, using a normality test. Continuous values were expressed in means and standard deviations when normally distributed while in medians and interquartile ranges when not normally distributed. For the values following normal distributions, t-tests was used and for values that did not follow a normal distribution, the Mann-Whitney test was used. Categorical variables were expressed with frequencies and percentages. Percentages were compared using the Fisher's Exact Test. The level of statistical significance was set at p value <0.05 for the comparisons between the groups. All the statistical analyses were performed using the IBM SPSS Statistics (V.22).

Results

Bodyweight Change

Bodyweight was measured with precision in all rats before the experiment and on the day of sacrifice. In the control group, the mean bodyweight of the rats decreased during the experiment and until sacrifice. This change was statistically significant (p=0.005). Similarly, in the chemotherapy (CT) group, a statistically signifi-

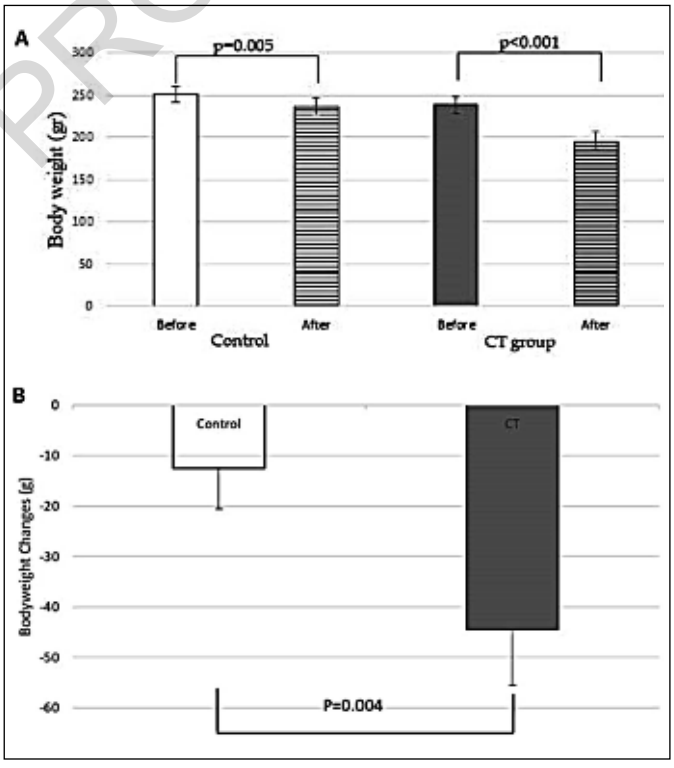

Fig. 1: Bodywight: A. Comparative bar chart of body Weight (gr). In the chemotherapy (CT) group, a decrease in the average bodyweight of the rats was observed during the experiment, significantly higher than the weight loss to the Control group. B. Comparative bar chart of Body weight changes. The decrease in bodyweight in the CT group was significantly increased than in the control group.

cant decrease in the average bodyweight of the rats was observed (p<0.001). The decrease in bodyweight in the CT group was significantly increased than in the control group (p=0.004) (Fig. 1).

No deaths ANASTOMOTIC DEHISCENCE
or wound infections occurred. All animals were sacrificed, and an autopsy took place on the seventh postoperative day. During the autopsy, a macroscopic examination was performed to check if there was any anastomotic dehiscence. The macroscopic examination showed no anastomotic dehiscence in the control group. In the chemotherapy group, 8 out of 20 rats (40%) had dehiscence, which occurred as peritonitis or anastomotic abscess. The anastomotic dehiscence in the chemotherapy group was statistically significant compared to the control group (p=0.02).

Bursting Pressure Measurement

The CT group showed statistically significantly lower values of bursting pressure compared to the control group (p<0.001). In the CT group, in 36% of the cases, the rupture was observed away from the anastomosis site, compared with 60% in the control group. These results, along with the locations of the ruptures in the two groups are described in Fig. 2. The rupture in the area of anastomosis was more common in the CT group than in the control group, with no statistical significance (p=0.168).

Adhesion Formation

There was a statistically significant difference in adhesion formation. In the control group, 30% of the rats did not show any adhesions whereas in the CT group all rats had adhesions assessed with at least grade 1 in the Van der Hamm's scale. In addition, in the CT group, 40% of rats showed grade 3 adhesions, compared to none in the control group. The incidence of varying degrees of adhesions is shown in Fig. 3. The control group showed statistically significantly fewer adhesions than the CT group (p<0.001).

Hydroxyproline

Hydroxyproline was measured as an indirect quantification of the amount of collagen in the area of anasto-

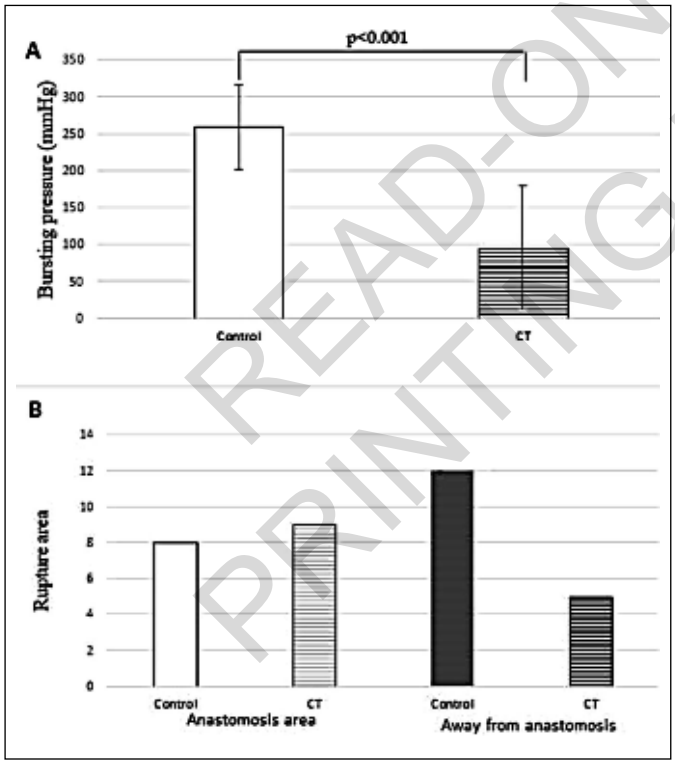

Fig. 2: Bursting pressure. A. Comparative bar chart of bursting pressure (mmHg). The CT group showed statistically significantly lower values of bursting pressure compared to the control group. B. Comparative bar chart of rupture area during bursting pressure. The rupture in the area of anastomosis was more common in the chemotherapy group than in the GH group, but it was not statistically significant.

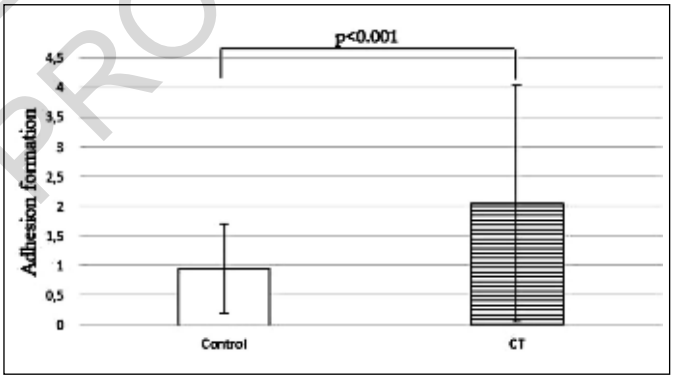

Fig. 3: Comparative bar chart of adhesion formation. The control group showed statistically significantly fewer adhesions than the CT group.

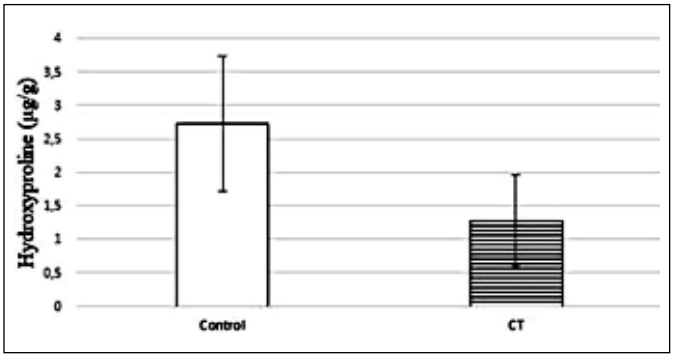

Fig. 4: Comparative bar chart of hydroxyproline (cmgr/mgr) tissues. the CT group showed a lower mean of hydroxyproline than did the control group, but not statistically significant.

mosis. The mean of hydroxyproline was calculated in the two groups, and the CT group showed a lower mean of hydroxyproline than did the control group which is not statistically significant (p=0.401). Fig. 4 summarizes the values of hydroxyproline.

Histological Assessment

The histological assessment of tissue healing included the following; inflammatory cell infiltration, neoangiogenesis, fibroblast activity and collagen deposition. Statistical analysis revealed significant changes in all histological parameters. Inflammation is significantly increased in the control group compared to the CT group (p<0.008). Similarly, neoangiogenesis (p<0.001), fibroblast activity (p=0.001) and collagen deposition (p<0.001) are all significantly increased in the control group compared to the chemotherapy group. Fig. 5 summarizes these results.

Discussion

Healing is a complex process that starts immediately after any tissue trauma with a final result of structural and functional tissue rehabilitation. Even though healing is a continuous process, it is divided into independent but overlapping phases. The most important is the inflammatory phase where defense mechanisms remove bacteria, necrotizing tissues and foreign bodies away from the trauma via phagocytosis. This leads to local preparation for collagen formation and deposition [28,29]. Any delay or inhibition of this phase will lead to improper healing process and inadequate tissue formation. Healing of colonic anastomosis presents with the same phases as any wound healing and is affected by the same local and systemic factors [30,31]. Failure of this process leads to dehiscence or rupture of the anastomosis, increasing postoperative morbidity and mortality. A major factor of quality of life in patients after resection of colon cancer is the rapid return to proper feeding. This is only feasible only after proper continuity of the gastrointestinal tract which is provided surgically. This, by its turn, is strictly related to the ability of the anastomosis to forward the intestinal content. Thus, it could be said that the success of the healing of the anastomosis is of outmost importance in the quality of life offered to these patients [28,32].

Colon cancer is the third most common malignancy worldwide and surgical resection remains the preferred therapy of choice. Anatomical continuity of the gastrointestinal tract is a necessary step for achieving quality of life in post-surgical patients. Cancer staging and grading are two basic parameters that determine prog-

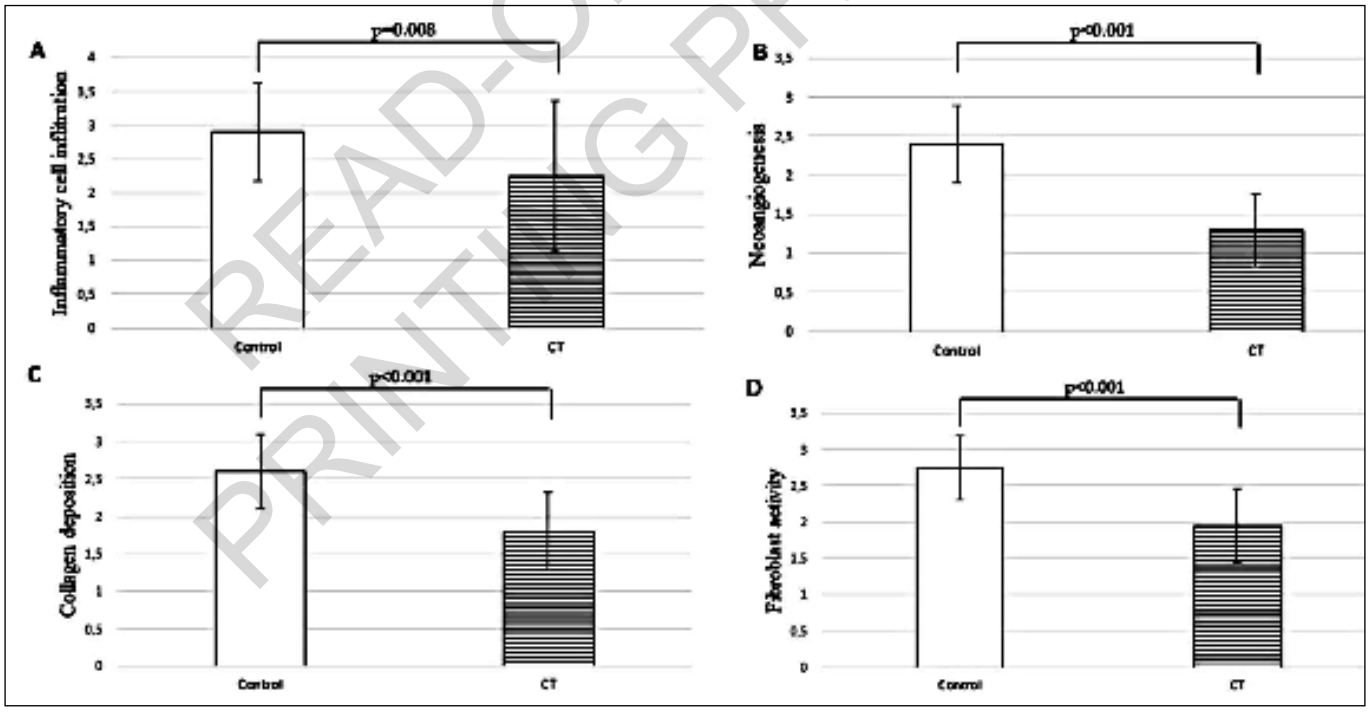

Fig. 5: Histological assessment. A. Comparative bar chart of inflammatory cell infiltration. A 0–4 Ehrlich and Hunt numerical scale was used for histological grading. There was a statistically significant difference between the two groups. B. Comparative bar chart of neoangiogenesis. A 0–4 Ehrlich and Hunt numerical scale was used for histological grading. There was a statistically significant difference between the two groups. C. Comparative bar chart of collagen deposition. A 0–4 Ehrlich and Hunt numerical scale was used for histological grading. There was a statistically significant difference between the two groups. D. Comparative bar chart of fibroblast activity. A 0–4 Ehrlich and Hunt numerical scale was used for histological grading. There was a statistically significant difference between the two groups.

nosis and long term survival. Lymph node or hepatic metastases have poor prognosis even though long tern survival may be feasible [10] . Thus, early diagnosis is of outmost importance. Apart from that, quality of life is related to the staging of the disease that frequently changes intraoperatively. 10% of patients with colon cancer are diagnosed with peritoneal carcinomatosis which is considered non treatable and has rather poor prognosis [33]. This is a terminal stage of cancer without cure and has a median survival of 5.2-6 months [34,35]. Patients with peritoneal carcinomatosis die due to intestinal obstruction, pain and cachexia. It has been proven that these patients have better survival rates if perioperative intraperitoneal chemotherapy is used [36,37]. The main advantage of the use of chemotherapy agents used intraperitonealy compared to intravenous administration is that the concentration of the drug used is higher in the area with possible residual disease and in the liver, due to possible haematogenic dispersion [28]. The direct administration of high dosage drug in the peritoneum and the direct effect on the liver, which is the main organ of micrometastasis through the portal vein, are the main advantages [10]. It has been reported that in patients with advanced colon cancer, intraperitoneal administration of 5-FU or in combination with systemic intravenous 5-FU is a safe practice with certain advantages, especially the decreased frequency of local recurrence [21,38,39]. In a randomized control trial which compared intravenous and intraperitoneal use of 5-FU in patients with advanced colon cancer, a statistically significant decrease was recorded in peritoneal metastases in patients with intraperitoneal administration of 5-FU [40]. Recently, a significant improvement of survival was recorded in adjuvant intraperitoneal administration of 5-FU after surgical resection of locally advanced colon cancer [41]. The combined use of intravenous and intraperitoneal administration of 5-FU postoperatively in patients with stage 3 colon cancer improved significantly survival and local recurrence [42]. In a multicenter randomized trial, stage 2 and 3 colon cancer patients who were administered intraperitoneally 5-FU for 6 days after resection, had significantly fewer local recurrence and chemotherapy was well tolerated [43]. The rate of local remission is reported lower and peritoneal implants are significantly reduced in peritoneal administration of 5-FU [23].

Despite the advantages of intraperitoneal distribution of chemotherapy, its immunosuppressive ability can have adverse effects on the healing of colonic anastomosis [22,23]. Huge differences in these effects have been published, possibly due to the various initial parameters; 5-FU dosage, start time and time period administered, co-administration of other cytostatics [19,23,32,44–49]. Reduced effect of 5-FU on anastomosis healing was recorded in short term period of 3-4 days or at delayed postoperative period [47,50]. Many studies had various parameters not equally established, like the time and the dosage that they were administered at, and others start the intravenous administration of 5-FU immediately postoperatively [25]. In our study, 5-FU dose was defined at 20mg/kg daily, which is the maximum tolerable dosage that can be administered and is considered equivalent to the daily administered dose in humans [45,48–52]. In addition, newer therapeutic agents, bleomycin and cisplatin, were decided to be administered simultaneously.

Adjuvant therapy of bleomycin seems to has positive results in remission and survival rates [19]. Unfortunately, it affects negatively the anastomoses by decreasing the production and deposition of collagen. It has been shown however that administration of bleomycin 3-4 days postoperatively does not affect the healing [19,20]. In our study, the bleomycin dose was 4mg/kg daily in a 2cc solution intraoperatively and postoperatively every day until sacrifice.

Cisplatin is a drastic agent in various neoplasms. Experimental studies have shown the satisfying response of small tumors when cisplatin was administrated intraperitonealy [18,53]. In our study, the cisplatin dose was 0,7mg/kg daily in a 2cc solution intraoperatively and postoperatively every day until sacrifice.

The effect of the chemotherapy agents was evaluated by recording the following parameters; rats' body weight, anastomotic dehiscence, burst pressure, adhesion formation, histological assessment and hydroxyproline levels.

Body weight loss postoperatively in rats that where administered cytostatics intraoperatively has been already published [32,47,48,50-52,54,55]. Weight loss per se does not seem to be affecting the anastomotic healing [51]. In our study, weight loss was observed in the chemotherapy group, which was statistically significant compared to the control group. Weight loss was observed in the control group too. Weight loss is possibly not only due to the effect of the procedure, but also to the immunosuppressive character of the drugs [47]. Other studies support that finding, reporting that weight loss per se does not affect the anastomosis, but the agents play significant role in that [51].

The probably most important indicator of insufficient anastomotic healing is the rate of anastomotic rupture and dehiscence [56]. Other studies report these complications to a significant percentage in rats who received intraperitoneal chemotherapy compared to control groups. Graf et al reported complications from the anastomoses at 12 out of 32 rats after the intraperitoneal administration of 5-FU [21]. More specifically perianastomotic abscess was observed in ten rats on the day of sacrifice while the rest two rats died from anastomotic rupture. In the control group only one test animal developed perianastomotic abscess postoperatively. Kanellos et al. showed similar results with anastomotic rupture in 6 out of 16 rats after the intraperitoneal administration of 5-FU while only one rat of the control group showed anastomotic rupture [48]. In the above two studies the 5-FU was administered intraperitoneal at a dose of 20 mg/kg of B.W. /day from the day of the surgery until

the seventh day postoperatively. On the contrary, Fukuchi et al in a similar study does not report a proportional increase in the frequency of anastomotic rupture in rats given 5-FU intraperitoneally but he mentions two deaths in the 5-FU group of rats without being able to adequately interpret this fact [57]. In our study, none of the control group's subject had an anastomotic rupture. In contrast, the chemotherapy group displayed a 40% anastomotic leakage with peritonitis/abscess formation. This difference is statistically significant and shows the negative effect of chemotherapy drugs in tissue healing.

Bursting pressure is a rather precise index of proper healing and mechanical stability of the anastomosis, because it depicts accurately the normal colon's function. Anastomotic rupture usually happens on the 4th postoperative day, when the healing process is in the most initial phase. It has been established that on the 7th postoperative day the burst pressure is significantly decreased in anastomosis where 5-FU was administered previously intraperitonealy [32,47-49,57,58]. In our study the administration of CT was for a course of 7 days. Similar studies have shown that even for a lesser period of administration (5 days or less), if the 5-FU administration started within the first 3 postoperative days, the burst pressure was significantly decreased [57,59-61]. Other studies claim that the burst pressure is not significantly decreased if the intraperitoneal use of 5-fu is limited in less than 5 days [45,50,62,63]. Measurement of bursting pressure in our study was performed on the 7th postoperative day and the chemotherapy group had significantly lower bursting pressure that the control group. Anastomotic rupture is associated with weak anastomosis and anastomosis in which the healing phase is still premature. This is why usually anastomotic ruptures are recorded during the 3rd or 4th postoperative day [64]. Rupture away from the anastomosis is associated with mechanically potent anastomosis and anastomosis in which the healing is in an advanced stage [32,64]. Comparing the two groups, rupture rate on the anastomosis in the chemotherapy group was increased, whereas on the control group was lower, however the difference was not statistically significant. While this result is not in accordance with similar research [57], the difference in the rupture area can be partly explained considering possibly the strength in the anastomotic tissues in control group compared to chemotherapy group. Adhesion formation is an expected result of normal response to surgical trauma and reformation of tissues. Adhesions normally have a positive effect on the healing process as they control possible small leakages and they provide a matrix for neoangiogenesis and thus better blood perfusion [48,49,65]. The initiation of the inflammatory reaction results in fibroblast activation and collagen deposition and it is related with the adhesion formation, the preservation of which is firmly connected to the fibrolytic mechanisms. Kanellos et al. found an increase of the adhesions in the 5-FU group of rats compared to the [32] same observation was shown by El-Malt et al as the intraperitoneal administration of 5-FU resulted in a larger number of adhesions in rats after 5 days of injection [63]. But this is not always the case, as there is a study where the administration of 5-FU resulted in the reduction of extent and severity of adhesions [62]. In our study, a significant increase of adhesions was recorded in the chemotherapy group compared to the control group. Possibly, the tissues try to minimize areas of small ruptures which are more often in the chemotherapy group due to the weakening of the anastomosis.

The adequacy of the mechanisms of the healing process is depicted by the collagen formation and deposition. The measurement of the amino acid hydroxyproline is a reliable method of defining the total collagen that is deposed in the subject area. The amount of collagen is considered rather important in the healing process, and experimental models of quantifying it have been introduced [28]. It is assumed that the chemotherapy drugs interfere with the fibroblast activity, decreasing fibroblasts' proliferation and functioning. Several studies that investigated the effect of chemotherapy drugs intraperitoneally showed a decrease on the levels of hydroxyproline [58-61]. Only one study observed an increase on the hydroxyproline [66]. Indeed, in the current study a decrease in hydroxyproline of the anastomotic area was recorded in the chemotherapy group compared to control, but the difference was not statistically significant.

As already mentioned, chemotherapy drugs through their immunosuppressive role can interfere with normal functions of macrophages and fibroblasts and they can negatively affect the anastomosis healing [41]. This results in reduced collagen synthesis with the appearance of toxic systematic reactions thus decreasing the neoangiogenesis and normal healing procedure. It seems that chemotherapy drugs can increase the inflammatory reaction. Many researchers after histological examination observed an increase in the proliferation and migration of other leukocytes in the anastomotic tissues after the administration of chemotherapy drugs [49,58,61-63]. However, in our study, number of leukocytes in the anastomotic tissues is significantly lower in the chemotherapy group compared to control. Similarly, the other histological findings of neoangeiogenesis, collage formation and fibroblasts are significantly lower in the chemotherapy group compared to control. This comes to accordance with the initial hypothesis and contiguous research [32,58,61].

Conclusion

In conclusion, the immediate postoperative intraperitoneal infusion of 5-FU, bleomycin and cisplatin affects negatively the healing process of the colon anastomoses. In fact, it affects the proliferation of fibroblasts and reduces the synthesis and deposition of collagen in the site of the anastomosis. As a result, the rate of rupture

is higher and their mechanical strength is lowered as it depicts by their bursting pressure. In addition, the inflammatory process is increased and the neoangiogenesis is decreased. It would be of researching interest the possible minimization of the adverse effects of the chemotherapy drugs, if a substance that could enhance the healing process could be co-administered with them.

Riassunto

È noto che i fattori chemioterapici influenzano la guarigione del paziente postoperatorio. Lo scopo del presente studio sperimentale era di valutare l'effetto dell'infusione intraperitoneale di 5-fluorouracile, bleomicina e cisplatino sulla guarigione delle anastomosi del colon nei ratti.

METODI: Quaranta ratti maschi Albino-Wistar sono stati divisi casualmente in due gruppi, un gruppo di controllo e un gruppo di chemioterapia (CT). In entrambi, è stata eseguita un'anastomosi del colon end-to-end. Nel gruppo di controllo, sono stati somministrati per via intraperitoneale durante l'operazione 2cc di una soluzione salina, e poi quotidianamente dopo l'intervento fino al sacrificio degli animali.

Nel gruppo CT, sono stati somministrati per via intraperitoneale durante l'operazione 2cc di una soluzione con 20 mg/ kg di peso corporeo di 5-fluorouracile, 4 mg/kg di peso corporeo di bleomicina e 0,7 mg/kg di peso corporeo di cisplatino, e successivamente quotidianamente dopo l'intervento fino al settimo giorno postoperatorio in cui furono sacrificati. Al sacrificio, è stata calcolata la presenza di aderenze e le anastomosi sono state resecate ed esaminate macroscopicamente. Sono state calcolate le pressioni di scoppio e sono state classificate le caratteristiche istologiche. Sono state valutate le concentrazioni di idrossiprolina.

RISULTATI: nessuna morte o infezione della ferita è stata osservata fino al sacrificio. Il peso corporeo è stato significativamente ridotto nel gruppo CT ($p = 0,005$). Le pressioni di scoppio ($p = 0,001$) erano significativamente più basse nel gruppo chemioterapico, mentre le aderenze erano significativamente aumentate ($p = 0,001$). Le concentrazioni di idrossiprolina non erano significativamente diverse ($p = 0,401$). Tutti i parametri istologici sono apparsi significativamente diminuiti nel gruppo CT: infiammazione ($p < 0,008$), neoangiogenesi ($p < 0,001$) e attività dei fibroblasti ($p = 0,001$) e deposizione di collagene ($p < 0,001$).

CONCLUSIONE: L'uso di agenti chemioterapici ha influito negativamente sul processo di guarigione dell'anastomosi del colon nei ratti. La diminuzione della risposta infiammatoria indica un più frequente rischio di deiscenza anastomotica, di rotture e perdita di peso corporeo dopo l'intervento.

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