# Effects of bromopride on abdominal wall healing with induced peritonealsepsis after segmental colectomy and colonic anastomosis in rats[I]

## Efeitos da bromoprida na cicatrização da parede abdominal com sepse peritonial induzida e submetidos à ressecção segmentar e anastomose do cólon esquerdo em ratos

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**ABSTRACT**

**PURPOSE**: Evaluate the effects of bromopride on abdominal wall healing of rats with induced peritoneal sepsis after segmental colectomy and colonic anastomosis.

**METHODS**: Forty rats underwent sectioning of the left colon and end-to-end anastomosis and were divided into two groups of 20 animals for the administration of bromopride (bromopride group - B) or saline solution (control group - C). Each group was divided into subgroups of 10 animals each to be killed on the third (GB3 and GC3) or seventh postoperative day (GB7 and GC7). It was analyzed the following characteristics: breaking strength of the abdominal wall's wound; surgical and histopathological features of the abdominal wall; and clinical features of the rats.

**RESULTS**: There was no difference between the groups in relation to the weight of the rats and the breaking strength of the abdominal wall's wound. The GB7 group presented less edema and less quantity of fibrin during histopathological evaluation compared to the GC7 group.

**CONCLUSION**: Bromopride did not have harmful effects on the healing of abdominal wall in rats.

**Keywords**: Wound Healing. Abdominal Wall. Dopamine Antagonists. Antiemetics. Rats.

**RESUMO**

**OBJETIVO**: Avaliar o efeito da bromoprida, na cicatrização da ferida operatória da parede abdominal de ratos com sepse peritoneal experimentalmente induzida e submetidos a ressecção segmentar e anastomose de cólon esquerdo.

**MÉTODOS**: 40 ratos distribuídos em dois grupos contendo 20 animais, para administração de bromoprida (grupo bromoprida- B) ou solução de NaCl 0,9% (grupo controle - C). Cada grupo foi dividido em subgrupos contendo 10 animais, para eutanásia no terceiro (GB3 e GC3) ou sétimo dia (GB7 e GE7) de pós-operatório. Os ratos foram submetidos à secção do cólon esquerdo e anastomose término-terminal. No dia da eutanásia foram avaliadas as características cirúrgicas da cavidade abdominal e clínicas dos ratos. Foram coletados segmentos da parede para a avaliação histopatológica e de resistência tênsil da ferida operatória.

**RESULTADOS**: Não houve diferenças entre os pesos dos ratos e resistência tênsil da ferida operatória nos dois grupos. Em relação a análise histopatológica, o grupo GB7 apresentou menos edema e menos fibrina que o grupo GC7. Não houve outras diferenças.

**CONCLUSÃO**: A utilização de bromoprida não resultou em distúrbios ou retardo da cicatrização no grupo de ratos submetidos à laparotomia e anastomose término-terminal em condições de sepse peritoneal.

**Descritores**: Cicatrização. Parede Abdominal. Antagonistas de Dopamina. Antieméticos. Ratos.

## Introduction

The use of antiemetic drugs is common in the postoperative period since nausea and vomiting are the most common complications after surgical procedures and general anesthesia. Nausea and vomiting affect 52% to 92% of patients undergoing operations and tend to occur on the first postoperative day[1,2].

There are three groups of antiemetic drugs that are grouped according to their mode of action. The antidopaminergic group has the highest reporting number of serious adverse events, but their use has growing up since the cisaprine was withdrawn from market. The dopamine antagonists bind to the dopamine's D2 receptor, an important receptor involved in the genesis of vomiting, and block its effect on the trigger zone, nucleus of the solitary tract and peripheral afferent pathways.

The bromopride has been used more frequently in pregnancy and childhood. In children there are reports of extrapyramidal releases. However, there are fewer reports of extrapyramidal release using the bromopride than using other antidopaminergic drugs, such as metoclopramide. Nonetheless, this fact does not reflect a minor side effect of bromopride but it reflects fewer studies about this drug than about metoclopramide[3]. It explains why bromopride is not sold in European countries and in the United States and confirms the need for experimental and clinical studies about this drug.

The surgical site infections are important causes of complications in the postoperative period and may be superficial, deep or cavity's. 38% of nosocomial infections are surgical site infections, and two thirds of them are superficial[4,5]. Infections tend to have a negative effect on wound healing, increasing oxidative stress and hindering the collagen's deposition[6-8].

The healing is a complex cellular and tissue process that involves three phases: the inflammatory, the proliferative and the remodeling. Any medication or condition that affects any component of this system will change it to a greater or lesser degree, helping or disturbing the final process of abdominal wall healing[9].

After an extensive review of the literature, there weren't found studies that assessed the effect of bromopride on the wound healing. Therefore, the objective of this study was to evaluate the Effects of bromopride on abdominal wall healing of rats with induced peritoneal sepsis after segmental colectomy and colonic anastomosis.

## Methods

This was an epidemiological study, analytical, mask, blind to the surgeon and to the pathologist.

Were used forty rats *Rattus norvegicus* albinos, Wistar, male. The rats had pre-operative age ranging from 90 to 120 days and preoperative weight ranging from 350g to 575g. During the preoperative period the rats were kept in cages containing five animals each, with a system of 12 hours of artificial light and 12 hours of darkness. The rats receive the standard diet with water *ad libitum*[10-12]. All the rats passed by the same operatory procedure. The rats were randomly divided into two groups.

The group bromopride (B) comprised 20 rats that receive subcutaneous doses of bromopride, 1mg/kg every 12 hours until the day of the kill. Moreover, this group was divided into two subgroups according to the date of the kill: GB-3, with rats sacrificed on the third postoperative day and GB-7, with rats sacrificed on the seventh postoperative day.

The control group (C) comprised 20 rats that received saline solution 0.9% administered subcutaneously in the postoperative period, every 12 hours until the day of the kill. Moreover, this group, was divided into two subgroups according to the date of the kill: GC-3, with rats sacrificed on the third postoperative day and GC-7, with rats sacrificed on the seventh postoperative day.

All surgical procedures were performed by the same surgeon who did not know which group the rats belonged. The anesthesia used was hydrochloride of xylazine 10 mg/kg and hydrochloride of ketamine 75 mg/kg. After anesthetics induction the animals were immobilized in supine position and then the trichotomy was performed just in the abdominal wall.

An incision of 4.0 cm in length was performed starting 1.0 cm above the external genitalia of the animal. The distal colon was exposed and it was performed a resection of 0.5 cm from the segment of the left colon, located 2.5 to 3.5 cm above the peritoneal reflection and it was anastomosed end-to-end with solid point, using 6.0 polypropylene thread.

Peritonitis was triggered by partial ligation of the cecum with 5.0 polypropylene thread, just below the ileocecal triangular fold, and with ten random perforations in the cecum done by a 40x13 needle[13].

The synthesis of the abdominal wall was performed in two planes by continuous suture with 3.0 silk's thread.

On the day to the kill, the rats underwent anesthesia and they were placed in supine position. It was made a rectangular resection of the abdominal wall with cuts 15 mm apart from

the initial laparotomy scar of the first surgical procedure. The rectangular segment of the wall was then divided into three parts with 30 mm wide and 23 mm in length each one. The third proximal to the chest was used to evaluate the breaking strength of the abdominal scar. The third distal to the chest was kept in 10% formalin and subsequently it was used to make slides for histopathological evaluation of the abdominal scar. The middle third was preserved in saline 0.9%.

The following features were considered during the work: preoperative weight, assessed on the day of the first operative procedure, postoperative weight, measured on the day of the kill of the rats, blocking of the cecum, apathy, diarrhea, erection of hair, hematoma, abdominal bloating, and feces in the cavity, all those assessed on the day of the kill.

The surgical evaluation of the abdominal cavity was performed by the surgeon during the kill of the rats. The variables presence of peritonitis, blocking cecum and abscess were graded as 0, absent, or 1, present.

The evaluation of the breaking strength of the abdominal wall's wound was performed with the aid of a digital Versa Test (Test Macmesin Versa, UK) coupled to a digital dynamometer AGF (Mecmesin Test Versa, UK). The third segment from the retangular abdominal wall retrieved from the rat proximal to the chest was fixed at the two ends of the equipment. During the determination of breaking strength it was adopted stringent care positioning and a standardization of the distance between a surgical scar and the collet. The speed used during the test 30 was mm/min[14]. The breaking strength of the abdominal scar was then expressed them in Newton (N).

The histopathological evaluation was done by a pathologist who did not know which group the rats belonged. The slides were made using the distal to chest third segment retrieved from the abdominal wall of the rats. The variables collagen, fibroblasts, mononuclear cells, polymorphonuclear cells, edema and neovascularization were graded: 0, absence, 1, little presence, 2, relative presence, 3, high presence. The variables abscess, foreign bodies and fibrin were graded: 0, absent; and 1, present.

Breaking strength results were compared by the nonparametric Mann-Whitney test. The results of histopathological evaluations were compared by Fisher's test. The results of the surgical evaluation of the abdominal cavity were also compared by Fisher's test. To compare the weights pre-and postoperatively it was used the Student t test.

This study's protocol was approved by the ethics committee for animal use (CEUA), from University of Brasilia (UnB).

## Results

One rat from the control group and one rat from the bromopride group, both to kill on the seventh day, were excluded from the study because they died in the immediate postoperative period with deaths not associated with the use of medications.

There was a statistically significant difference between the weights pre-and postoperative in all groups ($p \leq 0.001$).

The descriptive characteristics of the rats according to the groups which they belong are presented in Tables 1 and 2. No mouse had hematoma and abdominal bloating. There was no significant difference between the breaking strength of group bromopride (B) and group control (C).

**TABLE 1** - Descriptive features of the rats.

| | Day 3 | | Day 7 | |
|---|---|---|---|---|
| | **Bromopride** | **Control** | **Bromopride** | **Control** |
| Rats per subgroup (n) | 10 | 10 | 9 | 9 |
| Absence of peritonitis (n, %) | 1(10.0) | 0 | 0 | 0 |
| Blocking of the cecum (n, %) | 5 (50.0) | 3 (30.0) | 9 (100) | 9 (100) |
| Apathy | 3 (30.0) | 1 (10.0) | 2 (22.2) | 0 |
| Erection of hair (n, %) | 3 (30.0) | 1 (10.0) | 2 (22.2) | 0 |
| Diarrhea (n, %) | 0 | 1 (10.0) | 3 (33.3) | 1 (11.1) |
| Feces in abdominal wall (n, %) | 0 | 1 (10.0) | 0 | 0 |
| Foreign Body | 1.00 | 1.00 | 1.00 | 1.00 |
| Fibrin | 0 | 0 | 0* | 0* |

n-Number of rats; %-Percentage; *There was significant difference between fibrin in the bromopride and control groups with rats to kill in the seventh day.

**TABLE 2** - Mean ± Standard deviation from descriptive features of the rats of abdominal wall's wound.

| | Day 3 | | Day 7 | |
|---|---|---|---|---|
| | **Bromopride** | **Control** | **Bromopride** | **Control** |
| Preoperative weight | 403.30 ± 53.13* | 442.30 ± 37.56* | 492.78 ± 51.08* | 507.89 ± 45.01* |
| Postoperative weight | 421.00 ± 72.30* | 418.90 ± 46.93* | 433.33 ± 61.26* | 469.44 ± 59.17* |
| Breaking strength | 0.57 ± 0.61 | 0.35 ± 0.46 | 9.73 ± 5.63 | 11.66 ± 7.38 |

g-grams; N-Newton; M ± SD –; *Difference between pre and postoperative weights ($p \leq 0.001$).

There was a significant difference between subgroups bromopride and control, both to kill on seventh day (GB7 and GC7), in which the group bromopride had less edema (p=0.041) and less fibrin (p=0.041). The descriptive characteristics of the histopathological analysis are shown in Table 3.

**TABLE 3** - Median of the results of the histopathological analyzes. The variables collagen, fibroblast, mononuclear cells, polymorphonuclear cells, neovessels and edema were graduated from 0, absense, to 3, high presence. The variables abscess was graduated from 0, absent, to 1, present.

| | Day 3 | | Day 7 | |
|---|---|---|---|---|
| | Bromopride | Control | Bromopride | Control |
| Collagen | 0 | 0 | 1.00 | 1.00 |
| Fibroblast | 2.00 | 2.00 | 3.00 | 3.00 |
| Mononuclear cells | 2.00 | 2.00 | 3.00 | 3.00 |
| Polymorphonuclear | 1.50 | 2.00 | 3.00 | 3.00 |
| Neovessels | 2,00 | 2,00 | 2,00 | 3,00 |
| Edema | 2,00 | 2,00 | 1,00* | 1,00* |
| Abscess | 1,00 | 1,00 | 1,00 | 1,00 |

*There was significant difference between edema in the bromopride and control groups with rats to kill in the seventh day.

## Discussion

This is an original study. There are no national or international articles that evaluate the post operatory use of bromopride in any kind of surgery. However, it is important to say that this article analyzes the use of bromopride in a very specific condition: in the postoperative period of rats with induced peritoneal sepsis after segmental colectomy and colonic anastomosis.

It was chosen to analyze rats after segmental colectomy and colonic anastomosis, because these procedures are major trauma to the body compared to only exploratory laparotomies and they are very common procedures in coloproctology surgery.

Regarding the use of bromopride, colorectal specialists believe that bromopride have a greater effect than other antiemetic drugs in motility of the terminal ileum. However, this is an unproven scientific theory. According to this reasoning, the increased motility of the terminal ileum triggered by bromopride should mean an increase in the amount of adhesions. Adhesions should serve as a protective factor slowing the process of experimentally induced peritonitis through perforations. Nonetheless, the fact that bromopride and control groups did not show great statistical difference for the breaking strength and for clinical and surgical features suggests that this theory does not work in practice and bromopride does not act as a protective factor to peritonitis in post-surgery period.

It may be mentioned as one of the limiting factors of this study the technique of sepsis employed. This technique may evaluate both the role of bromopride in stimulating adhesion and in the decrease of the sepsis process. However, this technique to induce sepsis does not allow a good evaluation of the action of bromopride in the process of bacterial translocation.

Regarding the subgroups with rats to kill at day 7 after surgery (GB7 and GC7), the smallest amount of fibrin in the subgroup bromopride resulted in no decrease in breaking strength of the abdominal wall's scar. It may be explained by the fact that the fibrin acts more in the structural composition than in the increase of the strength of the tissue during the wound healing.

This is a limited study and it focuses coloproctology surgery. Further studies are needed to analyze the effect of bromopride in the clinical practice and in other types of surgery.

## Conclusion

Bromopride did not have harmful effects on the healing of abdominal wall in rats.

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