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The effect of ranitidine on postoperative infectious complications following emergency colorectal surgery: A randomized, placebo-controlled, double-blind trial

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Abstract. *Objective and Design:* To study the potential effect of ranitidine on postoperative infectious complications following emergency colorectal surgery. A randomized, placebo-controlled, double-blind trial was carried out in three university clinics and two county hospitals in Denmark. *Patients and Treatment:* One hundred and ninety-four consecutive patients undergoing acute colorectal surgery for perforated and/or obstructed large bowel were randomized in a double-blind fashion to receive ranitidine 100 mg i.v. twice a day commencing at induction of anesthesia and continued for five days (group I) or i.v. placebo (group II). All patients were given 1.5 g metronidazole plus 3.0 g cefuroxime at the time of surgery. Patients with perforation of the colon or rectum were given metronidazole and cefuroxime for further 3 days. All patients were assessed daily until discharge from the hospital. Thirty patients were withdrawn from the study (for reasons such as other diagnosis, refused to continue, medication not given as prescribed).
Main Outcome Measures: Patients were observed for signs of infectious complications; such as wound infection, intra-abdominal abscess, septicemia, and pneumonia.
Results: Both groups were similar with respect to age, sex, weight, duration of surgery, blood transfusions, and site of the procedure, as well as the histologic nature of the underlying disease process. However, the Mannheim Peritonitis Index (MPI) was significantly higher in group I compared with group II ($p < 0.05$). Wound infection, intraabdominal abscess, septicemia, and pneumonia were 12.9%, 5.2%, 3.8% and 14%, respectively in group I. In group II, the infectious complications were 16.1%, 6.8%, 6.9% and 22%, respectively. Twelve patients (13.8%) in the placebo group developed more than one complication compared with 5 patients (6.5%) in the ranitidine group.
Conclusion: Ranitidine may have a beneficial effect on postoperative infectious complications in patients following acute colorectal surgery.

Key words: Wound infection – Infectious complications – Ranitidine – Colorectal surgery – Immunology

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Introduction

Despite advances in the antibiotic treatment of aerobic and anaerobic bacteria, infectious complications remain a major cause of postoperative morbidity and mortality, particularly after emergency operations [1–5]. Transient impairment in immunocompetence is induced by major surgery, trauma, and burns [6–8], and preoperative and postoperative immunosuppression correlates with the risk of developing postoperative infectious complications [9–12]. The mechanism leading to trauma-induced immunosuppression is still only partially elucidated, but several peptides and suppressor molecules [13, 14] are thought to be involved in the process in which down-regulation of interleukin-2 (IL-2) production and release plays a key role [15, 16].

Hitherto, histamine has been considered primarily as an effector molecule in immediate hypersensitivity responses, but much evidence has accumulated to suggest that histamine is also a strong regulator of the immune system acting on specific histamine receptors expressed by immune competent cells [17–19]. It is well known that histamine is released from mast cells and basophils immediately after traumatic events [20, 21] and that it may be involved in the inflammatory response [17, 22].

Experimental studies have suggested that H_2 receptor antagonists (H_2RA) reduce trauma-induced immunosuppression [23] and improve IL-2 production [24]. We and others have previously shown that H_2RA's improve postoperative trauma-, blood transfusion- and sepsis-induced immunosuppression [23, 25, 26] and, therefore, the purpose of the present study was to evaluate the potential effect of perioperative ranitidine in reducing postoperative infectious complications after emergency colorectal surgery.

Patients and methods

The study was designed as a multicenter prospective randomized trial comparing ranitidine vs. placebo. Three university clinics and two county hospitals participated in the study. The study was carried out during the period April, 1991 to June, 1993.

Patient selection

Unless otherwise excluded all adult patients (aged 18 years or older) suspected of having either perforation or obstruction of the colon were considered. The diagnosis was based on the findings at operation. The criteria for exclusion were known allergy to the antibiotics used, or treatment with systemic steroids, non-steroidal anti-inflammatory drugs, H_2 receptor antagonists, cytostatic drugs, antiviral drugs and/or other known immunomodulating drugs within four weeks prior to surgery. Furthermore, patients treated with antibiotics within 24 h before the operation, and pregnant and lactating women were also excluded. Age, malignancy, surgical procedure, operation time, and intraoperative loss of blood, and perioperative blood transfusion were considered as possible risk factors for infections. Patients with peritonitis were evaluated using the Mannheim Peritonitis Index (MPI) [27]. Informed consent was obtained from all included patients and the study protocol was approved by the Ethics Committee of all participating hospitals according to the Declaration of Helsinki II.

Randomization and antibiotic administration

Patients were randomly allocated to the following two groups: group I received 100 mg ranitidine i.v. at induction of anesthesia and the same dose every 12 h for the next 5 days; group II received placebo at induction of anesthesia and continued as described for group I. Patients with intraoperative diagnosis other than perforation of the colon or large bowel obstruction were withdrawn from the study, as were patients who died within the first 48 h postoperatively. Patients entered the study in ascending numerical order, according to a randomization table.

Antibiotics

Patients with perforation of the colon or rectum were given 1.5 g metronidazole plus 3 g cefuroxime at surgery followed by 1 g metronidazole plus 1.5 g cefuroxime every 12 h for 3 days. Patients who underwent operation for large bowel obstruction without perforation were given 1.5 g metronidazole plus 3 g cefuroxime as "single dose prophylaxis". Cefuroxime was administered as a bolus, and the infusion time of 1.5 g metronidazole was about 60 min. No other antibiotics were given thereafter, unless an established infection was documented or a patient's clinical course was highly suggestive of developing septic complications.

Operative procedure

All anastomoses were conducted in two layers, using polyfilament sutures. Intra-abdominal drains, if used, were brought out separated from the main incision. Abdominal closure was conducted with either braided or monofile absorbable sutures. Subcutaneous drains were not permitted. Samples were taken from pus during drainage of abscesses and from blood if septicemia was suspected. The duration of the operation (time from skin incision to completion of wound dressing), intraoperative blood loss, and perioperative blood transfusion were recorded.

Definitions of surgical infections, mortality and follow-up

Patients were assessed daily until discharge from the hospital. Postoperative complications, cause of death, and the use of other antibiotics were recorded. Wound infection was defined as presence of pus, either discharged spontaneously or requiring drainage. Intra-abdominal abscess was verified by either surgical drainage or by ultrasound-guided aspiration of pus. Septicemia was defined as clinical symptoms of bacteremia with positive blood culture. Pneumonia was defined as a temperature above 38 °C and a positive X-ray examination. Patients whose treatment was not carried out in accordance with that stated in the protocol were withdrawn from the study. Skin sutures were removed primarily on the tenth postoperative day. Mortality was defined as death within 30 days of surgery. In all cases of death a careful examination of the course was made. All patients were examined before discharge from hospital and they were followed up in the outpatient clinic one month after surgery.

Recording and evaluation of data

Data were recorded on standard forms and entered for computer analysis. Differences between groups were assessed statistically using the chi-square test and Mann-Whitney U-test when appropriate. The 95% confidence limits for differences were calculated, $\alpha = 0.05$, $\beta = 0.20$.

Results

Thirty patients were withdrawn from the study (Table 1). Of the remaining 164 patients, 77 received ranitidine and 87 placebo. The two groups of evaluable randomized patients were well matched with respect to age, sex, height, weight, peritonitis and number of patients with colonic obstruction (Table 2). However, the MPI was significantly higher in the ranitidine group (median 23, range 15–42 compared with placebo, median 18, range 15–40, ($p < 0.05$). Diagnosis, surgical procedure, use of drains, operative time, loss of blood intraoperatively, and perioperative blood transfusion were equally distributed between the two groups (Table 3). Table 4 shows the infectious complications in the two groups. The frequency of wound infection, intra-abdominal abscess, septicemia, and pneumonia was 12.9%, 5.2%, 3.8% and 14%, respectively, in the ranitidine group and 16.1%, 6.8%, 6.9% and 22%, respectively, in the placebo group. There were no statistically significant differences between the individual complications in the two groups. In the placebo group 45 infectious complications occurred in 27 patients compared with 28 infectious complications in 21 patients in the ranitidine group. Twelve patients (13.8%) in the placebo group developed more than one complication compared with 5 patients (6.5%) in the ranitidine group (Fig. 1), chi-squares 2.2, $p = 0.14$, odds ratio = 0.39 (95% confidence limits 0.09, 1.59). Fascial rupture occurred in 4 patients in each group. Two patients in each group had

Table 1. Patients withdrawn after randomization.

	Ranitidine	Placebo
No. of randomized patients	98	96
Other diagnosis		
other G-I tumours	2	0
perforated ulcer	4	1
small bowel obstruction	2	2
appendicitis	0	1
Died within 48 h postoperatively	4	2
Refused to continue	2	1
*Prednisolone/H_2 blocker/other antibiotics	4	1
Medication not given as prescribed	3	1
Total number of withdrawals	21	9
Evaluable patients	77	87

* Randomized by a mistake.

Table 2. Pre- and perioperative data.

	Ranitidine	Placebo
No. of patients	77	87
Age	68 (18–82)	69 (18–79)
Sex (F/M)	43/34	52/35
Height (cm)	170 (145–189)	167 (170–190)
Weight (kg)	70 (42–110)	65 (37–116)
Concurrent diseases	28 (36%)	32 (37%)
Creatinine, micromol/L	80 (38–347)	83 (42–174)
Albumin, micromol/L	570 (242–756)	565 (219–706)
Hemoglobin, mmol/L	7.7 (5.4–11.5)	8.0 (5.1–11.5)
Number of patients with peritonitis	18 (23%)	22 (25%)
Number of patient with colonic obstruction	56 (72%)	59 (68%)

Table 3. Diagnosis and operation characteristics.

	Ranitidine	Placebo
No. of patients	77	87
Malignant tumour	57 (74%)	57 (66%)
No tumour	20 (26%)	30 (34%)
Surgical procedure		
right hemicolectomy	12 (16%)	17 (20%)
ileotransversostomy	1 (1%)	2 (2%)
left hemicolectomy	5 (6%)	8 (9%)
sigmoid resection	34 (44%)	33 (38%)
two or more procedures	13 (17%)	19 (22%)
colostomies only	12 (16%)	8 (9%)
Colostomies	42 (55%)	41 (47%)
Drain	35 (46%)	28 (32%)
Duration of surgery (min, median and range)	132 (30–270)	120 (30–300)
Intraoperative loss of blood (ml, median and range)	300 (50–1800)	300 (50–2700)
Perioperative blood transfusion (ml, median and range)	600 (0–1500)	600 (0–1500)

Table 4. Postoperative infectious complications.

	Ranitidine	Placebo
No. of patients	77	87
Infectious complications		
Abdominal wound infection	10 (12.9%)	14 (16.1%)
Intra-abdominal abscess/peritonitis	4 (5.2%)	6 (6.8%)
Septicemia	3 (3.8%)	6 (6.9%)
Pneumonia	11 (14%)	19 (22%)

anastomotic leaks which required re-operation. Seventeen patients died within one month after the primary operation (Table 5). Two patients died because of spread of tumour, 4 patients because of acute myocardial infarction, 4 patients following pulmonary or cerebral embolism, and 2 patients of pneumonia. Three patients died from multiorganic failure and 2 patients after re-operation for anastomotic leakage. There was no significant difference in mortality rate between the two groups. Postoperative death occurred between 3 and 31 days after the operation, with no difference between the two groups. Preoperatively, 1 patient in the placebo group (17%) who died had verified cardiac disease compared with 4 patients (36%) in the ranitidine group. The severity of the intra-abdominal disease evaluated by the MPI and current cardiac disease may explain the higher preponderance of death in the active group (Table 6) [28].

Discussion

Randomized controlled clinical trials are the preferred scientific method for comparing clinical efficacy of treatment strategies. Deviation from this standard (e.g. studies with historical controls, prospective studies without controls) have potential drawbacks. In particular, studies of acute abdominal surgery have major problems because of the heterogeneity of the patients. In order to overcome some of these problems only patients undergoing acute colorectal surgery were included, and a standardized recording was used and patients were evaluated with an index system.

The present study supports the observation that a considerable number of patients undergoing acute colorectal surgery still develop postoperative infectious complications despite adequate use of antibiotics [29, 30]. These findings suggest that a limit exists for the efficiency of antibiotics to reduce rates of postoperative infectious complications after colorectal surgery [4]. This view is further supported by the fact that a combination of systemic antibiotics plus topical application of antibiotics in wounds has failed to reduce rates of wound infection any further [31–34].

Furthermore, in a recent trial which assessed high risk patients undergoing colorectal surgery, prolonged antibiotic prophylaxis had no impact on surgical infections, not even when this was correlated with preoperative delayed type hypersensitivity (DTH) response [9]. The evidence that major surgical trauma impairs postoperative immunocompetence is substantial [23] and a reduction of postoperative infectious complications may be obtained by immunomodulating drugs [35].

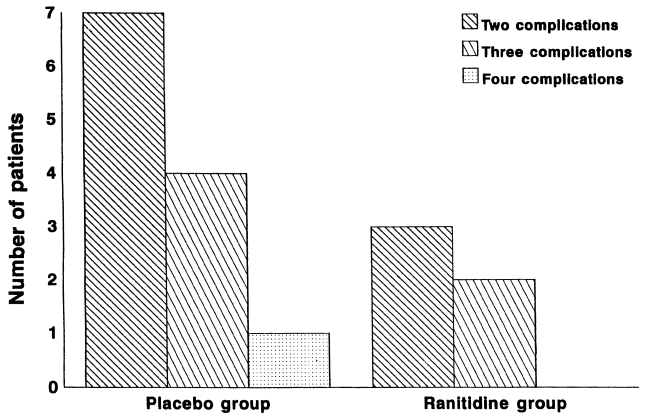

Fig. 1. Number of patients with two or more complications (wound infection, intraabdominal abscess, septicemia, pneumonia) after emergency colorectal surgery. Twelve patients in the placebo group developed more than one complication compared with 5 patients in the ranitidine group.

Table 5. Mortality.

	Ranitidine	Placebo
Number of patients	77	87
Mortality		
spread of tumour	1 (1.3%)	1 (1.1%)
AMI/cardiac failure	4 (5.2%)	–
pulmonary or cerebral embolism	1 (1.3%)	2 (2.2%)
pneumonia	1 (1.3%)	2 (2.3%)
multiorganic failure	2 (2.6%)	1 (1.1%)
anastomotic leakage	2 (2.6%)	–
Total number	11 (14.2%)	6 (6.9%) NS

NS = not significant.

When focusing on single infection parameters, the present study showed a trend in reduced rates of wound infection, intra-abdominal abscess, septicemia, and pneumonia in patients treated with ranitidine compared with those given placebo. Several factors may influence the interpretation of the results, e.g. intraoperative blood loss, presence of malignancy, duration of surgery, and spread of tumour. Blood transfusion impairs the immune function and increases the susceptibility to postoperative infectious complications [36, 37]. In the present study all patients received SAG-M blood [38] and there was no significant difference in intraoperative blood loss or perioperative amount of blood transfused between the two groups.

Patients with malignant tumours have a decreased immune response and hence an increased risk of postoperative infectious complications [23]. In the present study, the number of patients with malignant tumours was equally distributed between the two treatment groups, as was the number of patients with disseminated tumours. Perforation of the colon or rectum is a further risk factor, and this was also distributed equally between groups. However, the ranitidine group had a significantly higher MPI, i.e. more severely ill patients, compared with the placebo group, and this may explain the higher, but non-significant difference in mortality rate [28].

Table 6. Mannheim peritonitis index in 40 patients with perforation of the colon or rectum.

MPI	Placebo (n = 22)	Ranitidine (n = 18)
15	5	1
16	3	0
17	4	0
18	2	0
19	0	0
20	0	1
21	0	0
22	1	2
23	1	3
24	0	2
25	3	2
26	1*	1*
27	0	1
28	0	2**
29	1	1*
30	0	1*
> 30	1*	1*

*,** Postoperative death.

The exact mechanism by which histamine is involved in trauma-induced immunosuppression is not known. However, major operations appear to induce complement activation, specifically of the C3a and C5a subclasses, and endotoxin release, which subsequently may lead to enhanced histamine release by mast cells and basophils [39–41]. Histamine appears to be one of the important molecules regulating immune functions, as immunoactive cells express histamine receptors on their surface [17–19]. Histamine is an immunostimulant in physiological concentrations, acting primarily on H_1 receptors [17]. Increased concentrations, as observed during the early postoperative period and in the septic response [21, 40] are followed by binding to H_2 receptors [17, 23]. This seems to lead to suppression in several parts of the immune system by reducing lymphocyte blastogenesis, lymphokine production, antibody formation, NK-cell activity and granulocyte chemotaxis [17, 23, 42, 43], and by activating CD8+ suppressor lymphocytes [44].

Results from previous studies suggest that H_2 RA's may improve posttraumatic immune reaction [23, 25, 26], and therefore, it was anticipated that ranitidine would reduce postoperative infectious complications in the present study. However, the treatment lead to only marginal reduction in infectious complications compared to placebo. Among possible explanations may be a too short treatment course of only five days as infectious complications in colonic surgery often are observed from the 4.–10. postoperative day. Furthermore, the beneficial effect of H_2 RA on the immune system after perioperative whole-blood transfusion cannot be expected after transfusion with SAG-M blood as used in the present trial. The explanation may be less histamine release from transfused SAG-M blood compared with whole blood transfusion [37, 45].

In conclusion, H_2 receptor blockade may be of potential benefit as adjuvant treatment in major surgery to reduce postoperative immunosuppression and thereby postoperative infectious complications. No dose-response study in humans is available at present, but to date standard anti-ulcer doses

have been found to be effective in our studies evaluating immmunological effects in elective patients [23]. However, the effect of ranitidine in reducing postoperative infectious complications may be improved if administration of the drug is prolonged since recent studies have shown an extended immunosuppression following emergency surgery [46]. Results from the present and recent studies [47–49] seem to disprove the theories raised of enhanced risk of H_2 RA-induced pneumonia in critically ill patients. H_2 blockers should be evaluated as a potential treatment modality in acute surgery using a higher dose and prolonged treatment period [23].

References

[1] Roland M, Bergan T, Bjerkeset T, Erichsen H, Hoel R, Johansen S, et al. Prophylactic regimens in colorectal surgery: Comparisons between metronidazole used alone or with ampicillin one or three days. World J Surg 1985;9:626–32.

[2] DiPiro JT, Cheung RPF, Bowden TA Jr, Mansberger JA. Single dose systemic antibiotic prophylaxis of surgical wound infections. Am J Surg 1986;152:552–9.

[3] Moesgaard F. Wound infection following abdominal surgery. Prophylaxis and treatment. [thesis]. Copenhagen: Univ of Copenhagen, 1990.

[4] Solomkin JS, Dellinger EP, Christou NV, Busuttil RW. Results of a multicenter trial comparing imipenem/cilastatin to tobramycin/clindamycin for intra-abdominal infections. Ann Surg 1990;212:581–91.

[5] Dunn DL. Antibiotic tretment for surgical peritonitis. Ann Surg 1991;214:550–2.

[6] Antrum RM, Solomkin JS. Monocyte dysfunction in severe trauma: Evidence for the role of C5a in deactivation. Surgery 1986;100:29–37.

[7] Christou NV, Mannick JA, West MA, Kasper DL. Lymphocyte-macrophage interactions in the response to surgical infections. Arch Surg 1987;122:239–51.

[8] Athlin L, Holmberg SB, Hafström LO. Macrophage function and surgery. Eur J Surg 1991;157:163–70.

[9] Moesgaard F, Lykkegaard Nielsen M. Preoperative cell-mediated immunity and duration of antibiotic prophylaxis in relation to postoperative infectious complications. A controlled trial in biliary, gastroduodenal and colorectal surgery. Acta Chir Scand 1989;155:281–6.

[10] Hammer JH, Nielsen HJ, Moesgaard F, Kehlet H. Duration of postoperative immunosuppression assessed by repeated delayed type hypersensitivity (DTH) skin test. Eur Surg Res 1992;24:133-7.

[11] Wakefield CH, Carey PD, Foulds S, Monson JRT, Guillou PJ. Polymorphonuclear leukocyte activation. An early marker of the postsurgical sepsis response. Arch Surg 1993;128:390–5.

[12] Wakefield CH, Carey PD, Foulds S, Monson JRT, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. Br J Surg 1993;80:205–9.

[13] Ozkan AN, Hoyt DB, Tompkins S, Ninnemann JL, Sullivan JJ. Immunosuppressive effects of a trauma-induced suppressor active peptide. J Trauma 1988;28:589–92.

[14] Halpern MT. Human nonspecific suppressive lymphokines. J Clin Immunol 1991;11:1–12.

[15] Akiyoshi T, Koba F, Arinaga S, Miyazaki S, Wada T, Tsuji H. Impaired production of interleukin-2 after surgery. Clin Exp Immunol 1985;59:45–9.

[16] Rodrick ML, Wood JJ, O'Mahony JB, Davis CF, Gibic JT, Demling RH, et al. Mechanisms of immunosuppression associated with severe non-thermal traumatic injuries in man: Production of interleukin-1 and 2. J Clin Immunol 1986;6:310–7.

[17] Beer DJ, Rocklin RE. Histamine modulation of lymphocyte biology: Membrane receptors, signal transduction, and functions. Crit Rev Immunol 1987;7:55–91.

[18] Parsons ME. Histamine receptors: An overview. Scand J Gastroenterol 1991;26:46–52.

[19] Pearce FL. Biological effects of histamine: An overview. Agents Actions 1991;33:4–7.

[20] Lorenz W, Röher HD, Doenicke A, Ohmann CH. Histamine release in anaesthesia and surgery: A new method to evaluate its clinical significance with several types of causal relationships. Clin Anaesthesiol 1984;2:403–26.

[21] Sitter H, Lorenz W, Klotter HJ, Duda D, Buess G, Sattler J. Elevated plasma histamine concentration as a sensitive real-time parameter for distinct phases of the surgical trauma: A tool for technology assessment. Agents Actions 1991;33:203–7.

[22] Falus A, Meretey K. Histamine: An early messenger in inflammatory and immune reactions. Immunol Today 1992;13: 154–6.

[23] Nielsen HJ. The effect of histamine type-2 receptor antagonist on posttraumatic immune competence. Dan Med Bull 1995;42:162–74.

[24] Gifford RM, Tilberg AF. Histamine type-2 receptor antagonists immune modulation. II. Cimetidine and ranitidine increase interleukin-2 production. Surgery 1987;102:242–7.

[25] Adams W, Morris DL, Ross W, Lubowski D, Peters L. Cimitidine preserves immune function after colonic resection for cancer. Aust NZJ Surg 1994;64:847–52.

[26] Nielsen HJ, Mynster T, Jensen S, Hammer J, Nielsen H. Effect of ranitidine on postoperative change in soluble IL-2 receptor and CD8 molecules. Br J Surg 1994;81:1747–51.

[27] Wacha H, Linder MM, Feldmann U, Wesch G, Gundlach E, Steifensand RA. Mannheim peritonitis index - prediction of risk death from peritonitis: Construction of statistical and validation of an empirically based index. Theor Surg 1987;1:169–77.

[28] Billing A, Frölich D, Schildberg FW. Prediction of outcome using the Mannheim peritonitis index in 2003 patients. Br J Surg 1994;81:209–13.

[29] Juul P, Klaaborg KE, Kronborg O. Single or multiple doses of metronidazole and ampicillin in elective colorectal surgery. A randomized trial. Dis Colon Rectum 1987;30:526–8.

[30] Törnqvist A, Ekelund G, Forsgren A, Leander L, Olson S, Ursing J. Single dose doxycycline prophylaxis and preoperative bacteriological culture in elective colorectal surgery. Br J Surg 1981;68: 565–8.

[31] Moesgaard F, Lykkegaard Nielsen MC, Justesen T. Wound infection after intraincisional plus systemic antibiotic prophylaxis in an animal model. Eur J Clin Microbiol 1984;3:538–41.

[32] Juul P, Merrild U, Kronborg O. Topical ampicillin in addition to a systemic antibiotic prophylaxis in elective colorectal surgery. A prospective randomized study. Dis Colon Rectum 1985;28: 804–6.

[33] Moesgaard F, Lykkegaard Nielsen M. Failure of topically applied antibiotics, added to systemic prophylaxis, to reduce perineal wound infection in abdominoperineal excision of the rectum. Acta Chir Scand 1988;154:589–92.

[34] Moesgaard F, Nielsen ML, Hjortrup A, Kjersgaard P, Sorensen C, Larsen PN, et al. Intraincisional antibiotic in addition to systemic antibiotic treatment fails to reduce wound infection rates in contaminated abdominal surgery. A controlled clinical trial. Dis Colon Rectum 1989;32:36–8.

[35] Polk HC Jr. Non-specific host defence stimulation in the reduction of surgical infection in man. Br J Surg 1987;74:969–70.

[36] Jensen LS, Andersen AJ, Christiansen PM, Hokland P, Juhl CO, Madsen G, et al. Postoperative infection and natural killer cell function in patients undergoing elective colorectal surgery. Br J Surg 1992;79;513–6.

[37] Nielsen HJ. Detrimental effects of perioperative blood transfusion. Br J Surg 1995;82:582–7.

[38] Nielsen HJ, Hammer J, Moesgaard F, Kehlet H. Comparison of the effects of SAG-M and whole-blood transfusions on postoperative suppression of delayed hypersensitivity. Can J Surg 1991;34:146-50.

[39] Glovsky MM, Hugli TE, Ishizaka T. Anaphylatoxin-induced histamine release from human leukocytes: Studies of C3a leukocyte binding and histamine release. J Clin Invest 1979;64:804–11.
[40] Brackett DJ, Hamburger SA, Lerner MR, Jones SB, Schaefer CF, Henry DP, et al. An assessment of plasma histamine concentrations during documented endotoxic shock. Agents Actions 1990; 31:263–74.
[41] Frank MM, Flies LF. The role of complement in inflammation and phagocytoxis. Immunol Today 1991;12:322–6.
[42] Dohlsten M, Sjögren HO, Carlsson R. Histamine inhibits interferon-gamma production via suppression of interleukin-2 synthesis. Cell Immunol 1986;101:493–501.
[43] Bury TH, Corney JL, Radermacker MF. Histamine-induced inhibition of neutrophil chemotaxis and T-lymphocyte proliferation in man. Allergy 1992;47:624–9.
[44] Sansoni P, Silvermann ED, Khan MM, Melmon KL, Engleman EG. Immunoregulatory T-cells in man. Histamine-induced suppressor cells are derived from a Leu2+ (T8+) subpopulation distinct from that which gives rise to cytotoxic T cells. J Clin Invest 1985;75:650–6.
[45] Nielsen HJ, Hammer JH, Moesgaard, F, Kehlet H. Ranitidine prevents postoperative transfusion-induced depression of delayed hypersensitivity. Surgery 1989;105:711–7.
[46] Nielsen HJ, Witt K, Moesgaard F, Kehlet H. Ranitidine for improvement of delayed hypersensitivity response in patients with sepsis. Acta Chir Scand 1989;155:445–9.
[47] Fabian TC, Boucher BA, Croce MA, Kuhl DA, Janning SW, Coffey BC, et al. Pneumonia and stress ulceration in severely injured patients. A prospective evaluation of the effects of stress ulcer prophylaxis. Arch Surg 1993;128:216–21.
[48] Martin LF, Booth FV, Karlstadt RG, Silverstein JH, Jacobs DM, Hampsey J, et al. Continuous intravenous cimetidine decreases stress-related upper gastointestinal hemorrhage without promoting pneumonia. Crit Care Med 1993;21:19–30.
[49] Daon E, Summer W, Nelson S, Mason C. Cimetidine does not impair pulmonary clearance of *Pseudomonas aeruginosa* in normal rats. Dig Dis Sci 1994;39:1469–72.