# Effect of Histamine Blockade on Surgical Outcomes of Perforated Diverticulitis

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## Background

Diverticular perforation with peritonitis causes a significant host inflammatory response. Histamine, through H1 and H2 receptors, plays a critical role in the inflammatory cascade and the body's response to infection. Histamine is released by mast cells and basophils, and has a major role in the differentiation of monocytes into macrophages, all of which play a critical role in the immune systems response to peritonitis.

H1 blockers (diphendyramine) and H2 blockers (ranitidine) are used to treat pruritus and treat symptoms of gastroesophageal reflex. These medications are often prescribed by house staff at their patient's request, without thought that these medications may negatively impact patient outcomes. St Peter et al (2) have recently published data which suggests that children who received H1 or H2 blockade after perforated appendicitis had double the rate of intra-abdominal abscess formation. Those that got both H1 and H2 blockers had quadruple the rate of abscess formation. Interestingly, use of histamine antagonists had no effect on the rates of wound infections.

Due to the uncertainties about the use of histamine blockers, and their effects on the inflammatory response, the purpose of our study is to review their effects on patients who have undergone surgery for acute perforated diverticulitis.

## Results

A total of 86 patients were identified. 45 patients received histamine blockade postoperatively, and 41 patients did not. Table 1 shows the baseline patient demographics stratified by postoperative antihistamine use. Table 2 lists the perioperative variables that were examined and the study outcomes. There were 8 (9.3%) intra-abdominal abscesses and 13 (15.1%) wound infections. Hartmann's procedure was the most commonly performed operation (80%). Patients exposed to antihistamines had an increased rate of intra-abdominal abscess formation (15.6% vs. 2.4%).

**Table 1. Patient Demographics**

| | | Postoperative Antihistamine Use | | |
|---|---|---|---|---|
| | | No (N=41) | Yes (N=45) | P Value |
| Age (Mean±SD) | | 59±15 | 64±14 | 0.09 |
| Gender | Male | 39.0% | 44.4% | 0.61 |
| | Female | 61.0% | 55.6% | |
| Body Mass Index | | 29±5 | 30±6 | 0.79 |
| Preop Antihistamine | | 2.4% | 8.9% | 0.20 |
| Preop Steroid Use | | 14.6% | 15.6% | 0.91 |
| Preop WBC Count Abnormal | | 75.6% | 64.4% | 0.26 |
| Preop Hypotension | | 29.3% | 20.0% | 0.32 |
| Charlson Comorbidity Index | <=1 | 53.7% | 20.0% | 0.01 |
| | 2-3 | 9.8% | 17.8% | |
| | 4-4.9 | 19.5% | 35.6% | |
| | 5+ | 17.1% | 26.7% | |
| ASA Classification | 2 | 46.3% | 24.4% | 0.05 |
| | 3 | 43.9% | 51.1% | |
| | 4 | 9.8% | 24.4% | |

## Methods

A retrospective chart review from 2009-2010 was performed. Patients admitted to the hospital non-electively with a diagnosis of acute diverticulitis were identified using an administrative database. Patients requiring emergent operation for perforation or failing medical treatment were selected. Data was entered into a standardized database for analysis. The study was approved by the Lehigh Valley Hospital Institutional Review Board.

The primary study outcome measure was the presence of a post-operative abscess. Secondary outcomes were wound infection, mortality, ileus, and length of stay metrics. IBM SPSS Version 19 was used to perform the analysis. Student-t tests were used to compare means of continuous variables. Chi-squared analysis was used for categorical and binominal variables. Statistical significance was defined as $P \leq 0.05$.

**Table 2. Perioperative Variables and Outcomes**

| | | Postoperative Antihistamine Use | | |
|---|---|---|---|---|
| | | No (N=41) | Yes (N-45) | P Value |
| Operative Procedure | Hartmann's | 80.5% | 80.0% | 0.20 |
| | Sig resect, anas | 19.5% | 13.3% | |
| | Resect, anas, prox diversion | 0% | 6.7% | |
| Hinchey Classification | 1 | 29.3% | 33.3% | 0.98 |
| | 2 | 14.6% | 13.3% | |
| | 3 | 46.3% | 44.4% | |
| | 4 | 9.8% | 8.9% | |
| Mannheim Peritonitis Index | <=10 | 43.9% | 33.3% | 0.57 |
| | 11-14 | 19.5% | 31.1% | |
| | 15-16 | 19.5% | 22.2% | |
| | 17+ | 17.1% | 13.3% | |
| OR Time Over 3 Hours | | 19.5% | 24.4% | 0.58 |
| Intraop Transfusions (Mean+SD) | | 0.20±0.60 | 0.67±1.28 | 0.03 |
| Postop Abscess Formation | | 2.4% | 15.6% | 0.03 |
| Postop Wound Infection | | 14.6% | 15.6% | 0.90 |
| Postop PPI Use | | 56.1% | 26.7% | 0.01 |
| Antibiotic Regimen | Cipro/Flagyl | 9.8% | 2.2% | 0.34 |
| | Levaquin/Flagyl | 26.8% | 37.8% | |
| | Zosyn | 36.6% | 44.4% | |
| | Ancef/Flagyl | 2.4% | 4.4% | |
| | Ancef | 12.2% | 2.2% | |
| | Other cephalosporins | 4.9% | 4.4% | |
| | Others | 7.3% | 4.4% | |
| Duration of Antibiotic Use | | 9.39±5.08 | 11.42±5.05 | 0.34 |
| Days Until Liquid Diet | | 4.51±1.6 | 5.99±3.53 | 0.07 |
| Days Until Regular Diet | | 5.70±1.7 | 7.30±4.3 | 0.03 |
| ICU Length of Stay | | 0.83±1.63 | 4.02±6.08 | 0.001 |
| Length of Stay | | 10.66±5.07 | 14.20±7.82 | 0.02 |
| Mortality | | 2.4% | 4.4% | 0.61 |

## DISCUSSION

In our study, patients who received antihistamine blockade after surgery for acute diverticulitis had a statistically higher rate of intra-abdominal abscess formation. This corresponds to the findings of St Peter et al in perforated appendicitis. As in their study, histamine blockade had no effect on the rate of wound infections. The reason for this discrepancy is not clear. There is likely a fundamental difference in the pathogenesis of intra-abdominal abscess formation and wound infections. Methods of wound closure also vary, and were not examined in this study.

There are obvious limitations of this study. The retrospective nature of this study introduces a large potential for confounding variables to affect the primary study outcome (rate of abscess formation). The study groups had similar demographics except with respect to medical comorbidities. Patients with more medical problems may have been at higher risk for abscess formation that was not controlled for by this study. Intraoperative factors were similar between the two groups except with respect to intraoperative blood transfusion. This is a significant confounding variable. Blood transfusion is known to cause immunosuppression and increase infectious complications after colorectal surgery. Transfusion is related to higher rates of intra-abdominal abscess formation in patients with penetrating colon trauma.

Despite the limitations of this study, when coupled with other evidence from the literature, patients with peritonitis who receive histamine blockade seem to be at an increased risk for the development of intra-abdominal abscesses. There may be other variables that contribute to this increased risk. The need for intra-operative blood transfusion is certainly one of them. Physicians should consider these risks, versus the potential benefits, before prescribing antihistamines to this patient population, especially given that alternative medications (PPIs) exist for many clinical situations.

### References:

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