# Pentoxifylline as an adjuvant to surgery and antibiotics in the treatment of perforation peritonitis: a prospective, randomised placebo-controlled study

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## ABSTRACT

**Introduction: In animal models and human trials, pentoxifylline has shown beneficial pharmacological effects in the treatment of septic shock. We evaluated the role of pentoxifylline in the treatment of perforation peritonitis, as an adjuvant to surgery and standard antibiotic treatment.**

**Methods: A prospective, randomised placebo-controlled trial was conducted on 50 patients with perforation peritonitis. 25 patients were randomised to the test group and 25 patients to the control group. In addition to standard treatment, the test group of patients received pentoxifylline 200 mg per day as an adjuvant for three days. The endpoints of the study were to evaluate the condition of the wound in the post-operative period, APACHE II score and total duration of hospital stay.**

**Results: Both groups were comparable in all aspects. There were 23 male and two female patients in the test group, and 20 male and five female patients in the control group (p-value is 0.021). Mean age was 37.9 +/- 10.5 years in the test group and 33.8 +/- 11.0 years in the control group (p-value is 0.186). The APACHE II score in the test group and in the control group was statistically not significant (p-value is 0.661). In the test group, seven (28 percent) patients had wound infection and in the control group, 13 (52 percent) patients had wound infection (p-value is 0.083). The mean postoperative hospital stay in the test group was 6.8 +/- 2.1 days and in the control group, it was 11.2 +/- 5.2 days (p-value is 0.001).**

**Conclusion: Pentoxifylline improved the outcome by significantly decreasing the length of the hospital stay and the rate of wound infection.**


**Keywords: pentoxifylline, perforation peritonitis, septic shock, surgical complications, wound infection**

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## INTRODUCTION

Secondary bacterial peritonitis due to perforation of a hollow viscus is the most common form of peritonitis.[1] The standard treatment of secondary peritonitis due to bowel perforation includes resuscitation, antibiotics, exploratory laparotomy and closure of perforation, and continued postoperative support.[1] However, the mortality rate is still in the range of 10%–40%.[2,3] Pentoxifylline [3,7-dimethyl-1-(5-oxohexyl) xanthine] is a methylxanthine derivative with significant haemorrheological properties (promotes erythrocyte deformability, reduces blood viscosity and peripheral vascular resistance, decreases platelet aggregation and decreases plasma fibrinogen), and thus improves peripheral circulation and promotes blood flow.[4] It was used for treatment of intermittent claudication with mixed results. Subsequently, it was found to have a protective effect in infection of Gram-negative sepsis, peritonitis and meningitis in animal models.[5-8] It was also found to have the property to block the inflammatory action of interleukin-1 (IL-1) and tumour necrosis factor (TNF-$\alpha$) on neutrophils, and is thus was able to diminish the tissue damage caused by neutrophils in morbid conditions like septic shock and adult respiratory distress syndrome (ARDS).[9-12] In addition, pentoxifylline inhibits platelet and granulocyte function.[13] It also reduces fibrinogen concentration which increasing fibrinolytic activity.[14]

Pentoxifylline has been shown to improve the survival of animal models in experimental peritonitis and effect a significant reduction of adhesions and abscess formation in the peritoneal cavity.[6] In one clinical trial, it showed beneficial effects in patients with perforation peritonitis in terms of shortened hospital stay, improved Acute Physiology And Chronic Health Evaluation-II (APACHE-II) score postoperatively and decreased incidence of wound infection.[15] The present study was designed to determine and evaluate the role of pentoxifylline as an adjuvant to surgery and antibiotic treatment for perforation peritonitis in terms of incidence of wound infection, APACHE-II score, and the length of hospital stay.

**Table I. Patient demographics and presentation.**

| | Test group (n = 25) | Control group (n = 25) | p-value |
|---|---|---|---|
| Gender (%) | | | |
| Male | 23 (92) | 20 (80) | 0.021* |
| Female | 2 (8) | 5 (20) | |
| Mean age ± SD (years) | 37.88 ± 10.51 | 33.80 ± 10.99 | 0.186** |
| Associated systemic disease | MI (1)<br>Br. asthma (1)<br>Epilepsy (1) | MI (1)<br>PTB (1) | 1.000* |
| No. smoking (%) | 17 (68%) | 13 (52%) | 0.248* |
| No. APD (%) | 4 (16%) | 2 (8%) | 0.66* |
| No. NSAID intake (%) | 5 (20%) | 9 (36%) | 0.345* |
| Mean duration of peritonitis ± SD (days) | 2.29 ± 1.25 | 2.64 ± 1.32 | 0.596** |
| No. tachycardia (pulse > 90/min) (%) | 16 (64%) | 21 (84%) | 0.209 |
| No. shock (SBP < 90 mmHg) (%) | 3 (12%) | 5 (20%) | 0.699 |
| No. abnormal renal function (%) | 9 (32%) | 9 (36%) | 0.765 |
| No. abnormal ABG (%) | 7 (28%) | 11 (44%) | 0.238 |
| No. abnormal haematocrit (%) | 9 (36%) | 8 (32%) | 0.765 |

*Chi-square test; **_t_-test
Test group: pentoxifylline group; Control group: normal saline group; SD: standard deviation; MI: myocardial infarction; PTB: pulmonary tuberculosis; APD: acid peptic disorder; SBP: systolic blood pressure; ABG: arterial blood gas analysis

## METHODS

After ethical clearance from the institute's ethics committee and full informed consent was obtained from all the patients, the study was conducted in a prospective, randomised placebo-controlled manner. The study was conducted in the Department of General Surgery of Nehru Hospital at the Post Graduate Institute of Medical Education and Research, Chandigarh, India, over a period of one year from January 2005 to December 2005. Initially calculating a prevalence of 10% wound infection rate in perforation peritonitis, 48 patients were planned to be recruited in each arm of the study with a 95% confidence interval and a power of 80%. But due to time and logistic constraints, we could only recruit 25 patients in each arm of the study. 50 consecutive patients with clinical and radiological diagnosis of perforation peritonitis were admitted into the surgical emergency department. Inclusion criteria were: (a) patient's age 13–60 years; (b) clinically diagnosed and radiologically-confirmed gastrointestinal perforation with air under the diaphragm on the erect chest radiograph; and (c) patients undergoing standard surgical management for perforation peritonitis with laparotomy, closure of perforation and lavage together with routine postoperative antibiotic treatment. Exclusion criteria were: (a) patients with clinically and radiologically-proven sealed-off perforation; (b) patients being managed conservatively; (c) patients not accepting randomisation; (d) any inadvertent event necessitating a major change in the treatment protocol; (e) any clinical deterioration of the patient; (f) patients having adverse reactions to pentoxifylline such as vomiting, high fever or cardiovascular disturbances; and (g) patients with preoperative APACHE-II scores of more than 16.

All patients were evaluated and resuscitated in the emergency department. Once the patient was planned for surgery, the patient was randomised into the test or control group by using a computer-generated random number pattern. Both the patient and the surgeon were blinded to the randomisation. All the preoperative data was recorded in a prospective manner and the preoperative APACHE-II score was calculated to assess the physiological reserve of the patient. In the test group, pentoxifylline 200 mg per day as an infusion in 500 ml of normal saline over a period of 3–4 hours was given from the preoperative period and continued for three days postoperatively. The patient was operated upon only when haemodynamically-stable and had an adequate urine output. All surgeries were performed under general anaesthesia by a surgical registrar. All the gastric and duodenal perforations were primarily closed by omental patch reinforcement. The ileal perforations were closed in two layers, the inner seromuscular with absorbable 3-0 suture in an interrupted manner, and the outer serosal layer was closed by interrupted non-absorbable 3-0 suture. Postoperatively, all patients received antibiotics, usually consisting of a third generation cephalosporin along with aminoglycosides and metronidazole. In addition, antisecretory agents ($H_2$-receptor antagonist/proton pump inhibitors),

**Table II. Outcome measures.**

| | Test group | Control group | p-value |
|---|---|---|---|
| Mean APACHE-II score ± SD (range) | | | |
| Preoperatively | 5.24 ± 3.126 (1–15) | 5.64 ± 3.29 (0–14) | 0.661* |
| Postoperatively | 2.08 ± 1.80 (0–5) | 2.36 ± 1.91 (0–7) | 0.597* |
| No. wound status (%) | | | |
| Healthy | 18 (72) | 12 (48) | 0.083** |
| Infected | 7 (28) | 13 (52) | |
| Superficial | 4 (16) | 6 (24) | 0.633** |
| Deep | 1 (4) | 2 (8) | |
| Burst | 2 (8) | 5 (20) | |
| Mean hospital stay ± SD (range) (days) | 6.84 ± 2.11 (4–12) | 11.20 ± 5.2 (5–26) | 0.001* (t = 3.787) |

*t-test; ** chi-square test.

analgesics and *Helicobacter pylori* medications were given, when indicated. The patients in the test group received pentoxifylline on postoperative days one and two as infusion, as described. The patients in the control group received normal saline instead of pentoxifylline as a placebo.

Postoperatively, the primary dressing was changed at 48 hours (earlier if soakage was present). Wound inspection was done on a daily basis throughout the hospital stay to look for the presence or absence of wound infection. The APACHE-II score was recorded in both groups on postoperative day three for comparison. Patients were discharged once they were ambulatory, afebrile, accepting and tolerating a solid diet and having good bowel movement. The length of hospital stay was recorded on the day of discharge. Data analysis was done using the Statistical Package for Social Sciences version 10 (SPSS Inc, Chicago, IL, USA). The outcome measures of the test and control groups were compared, and a p-value of $< 0.05$ was considered to be statistically significant. Continuous data was expressed as mean with standard deviation, with calculation of the probability value to measure the significance of difference. Continuous variables were compared by Student's *t*-test. Binary variables were tested by two-tailed chi-square test.

## RESULTS

The study population consisted of 50 patients, with 25 patients receiving adjuvant pentoxifylline and 25 patients receiving normal saline as placebo. Both groups were comparable in demographical characteristics, preoperative symptoms and surgical findings (Table I). The mean age in the test group was 37.88 years, with a standard deviation of 10.51 years, while it was 33.80 ± 10.99 years in the control group ($p = 0.186$). The male:female ratio in the test group was 23:2, and in the control group it was 20:5. The mean duration of peritonitis was 2.29 ± 1.25 day in the test group, and 2.64 ± 1.32 days in the control group ($p = 0.596$). Three patients in the test group and two patients in the control group had associated systemic disease. Three patients (12%) in the test group and five patients (20%) in the control group presented in a state of shock (defined as a recordable systolic blood pressure of less than 90 mmHg). Renal function was deranged in 32% of patients in the test group and 36% in the control group. 28% of the patients in the test group and 44% in the control group had abnormalities in the arterial blood gas analysis. Abnormal haematocrit was seen in 36% of patients in the test group and 32% of patients in the control group.

The mean preoperative APACHE-II score was 5.24 ± 3.126 in the test group, and 5.64 ± 3.29 in the control group. The postoperative APACHE-II score was 2.08 ± 1.80 and 2.36 ± 1.91 in the test and control groups, respectively. The difference was not statistically significant ($p = 0.661$) (Table II). Four patients in the test group had gastric perforations and 21 (84%) patient had duodenal perforations. In the control group, four patients (16%) had gastric, 18 patients (72%) had duodenal and three patients (12%) had ileal perforations. Wound infection was present in a total of 20 patients (40%), seven (28%) in the test group, and 13 (52%) in the control group. Wound infection was categorised into superficial wound infection (defined as presence of erythema or pus discharge from the wound) and deep wound infection (defined as presence of slough in the wound with or without a burst abdomen). Of the 13 patients in the control group who developed wound infection, six had superficial wound infection and two had deep wound infection. Though the wound infection was more common in the control group (52%) when compared to the test group (28%), the difference was not significant ($p = 0.083$) (Table II). Three patients in the control group had intra-abdominal pus collection postoperatively during the hospital stay but it was managed by ultrasonologically-guided percutaneous pigtail catheter drainage. No patient in the test group had this problem. This was statistically significant ($p < 0.05$). The mean postoperative hospital

stay in the test group was 6.84 ± 2.11 days, compared to 11.20 ± 5.2 days in the control group. The difference was highly significant statistically (p = 0.001), with a lower hospital stay in the test group (Table II).

## DISCUSSION

Pentoxifylline has been used for various vascular problems, including peripheral vascular disease, impaired cerebral blood flow, labyrinthine disorders, vasoocclusive crises, disorders of ophthalmic circulation and asthenozoospermia.[4] Both experimental and clinical trials have shown its effectiveness in the treatment of serious infective conditions, such as Gram-negative sepsis, perforation peritonitis, meningitis and ARDS.[5-8] The immunomodulatory and inhibitory actions on various cytokines, primarily TNF-α and IL-1 effects along with the haemorrheological properties, have been attributed for improved microcirculation, ultimately leading on to better outcome.[9] Bailly et al demonstrated synergism of pentoxifylline with antibiotics, mainly fluoroquinolones especially ciprofloxacin in the inhibition of TNF-α.[16] Fazely et al showed pentoxifylline to decrease HIV-1 replication in acutely infected human mononuclear cells and augment the efficacy of azidothymidine and ameliorate TNF-induced cachexia.[17] Another study has shown pentoxifylline to alter the course of ARDS and multiorgan dysfunction syndrome in septic shock, by reducing clinical recovery time, morbidity and mortality.[10]

In our study, we used pentoxifylline as adjuvant to standard surgical management strategy in clinically-diagnosed and radiologically-confirmed patients of perforation peritonitis. The recommended dosage for intravenous administration ranges from 200 mg to 1,200 mg/day in divided doses as an infusion.[4] We adopted the lowest dosage regimen of 200 mg intravenous infusion daily for three days. The reported side effects of pentoxifylline after intravenous administration were primarily cardiovascular, such as tachycardia, flushing and hypotension, with others being high fever and vomiting.[8,18] None of the 25 patients who received pentoxifylline had side effects in our study. The proposed mechanism of the action of pentoxifylline in perforation peritonitis is complex. It increases the inherent fibrinolytic activity of the peritoneum and it reduces the fibrinogen levels, resulting in reduction of fibrin deposition, inhibition of formation as well as expansion of fibrin clots, thus preventing entrapment of bacteria in fibrin and accelerated bacterial clearance by preventing thrombosis of subperitoneal lymphatic and inhibitory effect on subclinical disseminated intravascular coagulation that accompanies severe peritonitis and septic shock.[6] Other beneficial effects include improvement in microcirculation, increased bactericidal effects of chemotherapeutic agents by improved microcirculation, increased transmembrane permeability into bacterial cells,[15] and physiological changes in fibroblasts contributing to better wound healing.[8]

The best available method of risk stratification in patients with intra-abdominal infection is the APACHE-II scoring system which is even recommended by the surgical infection societies.[1,18] Bohnen et al, in his study correlating APACHE-II scores and mortality in patients with intra-abdominal infection, showed increased mortality rate in patients who had a mean APACHE-II score of 18.9.[19] Pacelli et al documented a mortality rate of 2.7% in patients with an APACHE-II score of 0–10 in comparison to patients with a score of 11–20 and a mortality rate of 30.3%.[20] In our study, we enrolled only patients with preoperative APACHE-II scores of < 16 and used APACHE-II scores for group comparison, postoperative complications, as well as drug trials. We found that in both the test and control groups, APACHE-II scores decreased significantly postoperatively (p = 0.000 in both groups). There was no significant difference between the two groups (p = 0.597).

Svanes et al documented significant increased adverse effects and complications in delayed perforation peritonitis of more than 12 hours' duration.[21] The mortality increased by 7–8 times, complications by three times, and length of hospital stay by two times in delayed perforation peritonitis. In our study, there was an increased incidence of wound complications in patients who presented with peritonitis of more than one day's duration (57.1%), when compared with patients of less than one day's duration of peritonitis. The wound infection was present in 28% of patients in the test group, as compared to 52% in the control group. No significant difference between the two groups was found, when preoperative APACHE-II scores and wound infection were compared together. We also found a significant decrease in the mean length of hospital stay in the test group (6.8 days) compared to the control group (11.2 days). Length of hospital stay was also examined after excluding those patients with intra-abdominal pus collections: in the control group, the length of hospital stay was 9.7 days, compared to 6.8 days in the test group (p < 0.001).

Shukla et al used pentoxifylline as an adjuvant in the treatment of perforation peritonitis and showed that pentoxifylline could significantly improve APACHE-II score, decrease the length of hospital stay (mean 8 days, compared to 11 days) and decrease the incidence of wound infection (6/18 patients, compared to 12/18).[15] 61% of the patients in this study had typhoid enteric perforations, 9% had gastric and 31% had duodenal perforations. In our

study, 78% of patients had duodenal perforations, 16% patients had gastric and only 6% had ileal perforations. There was a significant decrease in the length of hospital stay and a relatively decreased incidence of wound infection in the test group, when compared to the control group. The postoperative APACHE-II scores in both the test and control groups decreased significantly, when compared with the respective preoperative APACHE-II scores, but the difference between the two groups was not statistically significant. This study showed that pentoxifylline significantly improves the outcome of perforation peritonitis by decreasing the length of the hospital stay and the rate of wound infection. However, it must be noted that the small sample size of this study gave rise to a type II statistical error in the data analysis. A larger study with randomisation is needed for better evaluation and to minimise the type II statistical error.

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