# Metronidazole in Anaerobic Surgical Infections

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## Abstract

Fifty acute surgical cases were treated with Metronidazole where mixed growth of anaerobic and aerobic bacteria was isolated in a trial conducted in North Surgical Ward, Mayo Hospital. Satisfactory results were obtained in majority of cases treated with combination therapy of Metronidazole and broad spectrum antibiotics. Furthermore the post-operative wound infection was reduced considerably thus shortening the convalescence and stay period in hospital. The side effects were few and not of serious consequence. These results were compared With similar surgical procedures without the use of Metronidazole. It was found that Metronidazole produces marked reduction in the profile of post-operative complications when used in combination with other antibiotics effective against aerobes. Metronidazole has no effect against aerobic infections (JPMA 32:201, 1982).

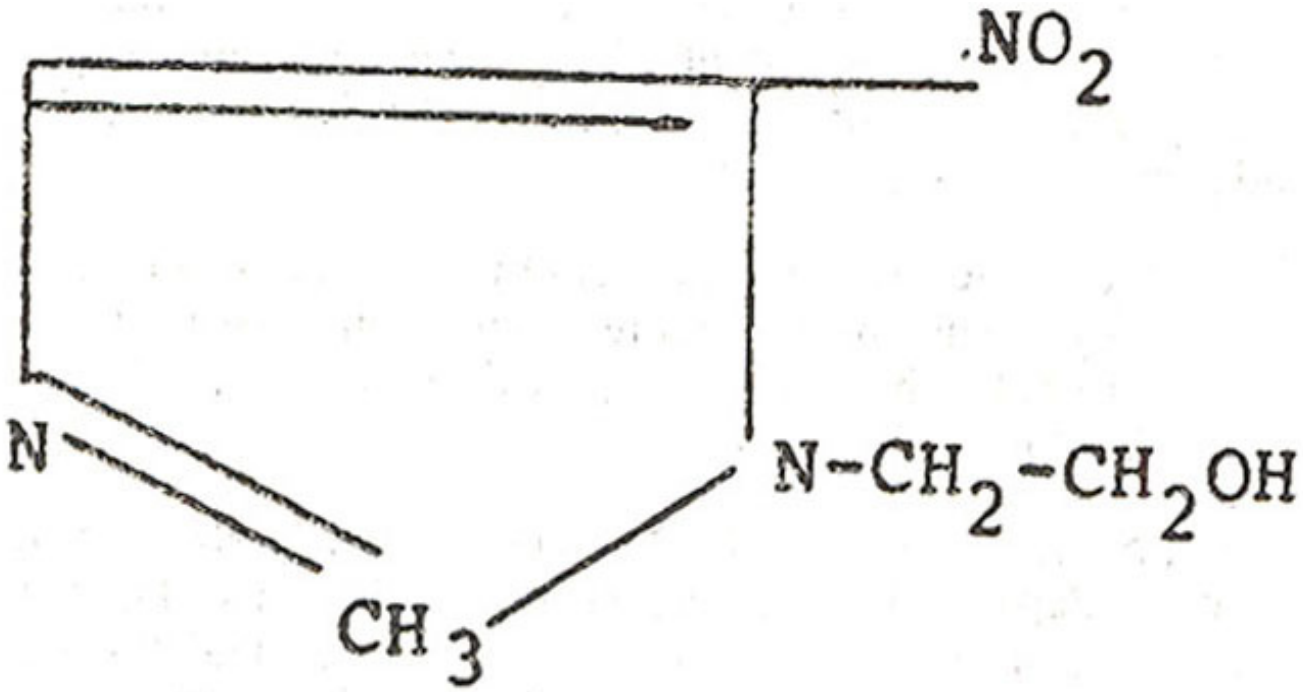
## Introduction

Metronidazole was first introduced in the treatment of infections caused by Trichomonas vaginalis (Gosar and Julou, 1959)1. Later on it was reported to be effective in the treatment of Vincent's gingivitis (Shinn, 1962) and a variety of other diseases, like tropical ulcers, amoebic dysentery and amoebic liver abscess (Buck etal., 1978). It was also found to be effective in the treatment for infections by anaerobic bacteria, particularly Bacteroides species.

The drug is well absorbed from the gastrointestinal tract. It has a wide range of bactericidal activity against a number of anaerobic bacteria.

After administration, 20% of the drug is bound with plasma and is not effective biologically. The remaining 80% is in free form and acts as an antimicrobial agent. It is partly metabolized in the liver (Ings et al., 1966) showed that approximately 60-70% of the drug is excreted unchanged in the urine. The kidneys are the main organ from where elimination takes place. The plasma half life is 6-8 hours and a single 200 mg oral dose produces a mean peak level of 5 ug/ml at 1-2 hours, falling to lug/ml after 24 hours (Welling and Munro, 1972). Single doses of Ig and 2.4g produce peak levels of about 26 and 45 ug/ml respectively. Biliary tract is not the route of excretion though therapeutic levels may be achieved in bile (Lykkegarrd et al., 1977). Normally intestinal flora is not markedly changed by the drug hence it is unlikely to cause vitamin deficiencies. It enters all tissues of the body and is present in the liver, breast milk, amniotic fluid and C.S.F. Metronidazole has been shown to inhibit the electron-transport system in Trichomonas vaginalis which probably explains its selective action against anaerobic bacteria (Edwards and Mathison, 1970).

The object of the trial was to assess that:




Metronidazole is (I - (2-Hydroxyethyl) 2-Methyl-5-Nitromidazole

The drug is well absorbed from the gastrointestinal tract. It has a wide range of bactericidal activity against a number of anaerobic bacteria.

1. In surgical practice anaerobes are a very important cause of sepsis and are mostly of endogenous origin.
2. The administration of Metronidazole in the pre and immediate post-operative period plays a more vital role than waiting for infections to get established and then start the drug.
3. Due to obvious difficulties of anaerobic culture and urgency of correct treatment in serious cases anaerobic infections should also be diagnosed clinically i.e., by the presence of foul smelling pus and resistance to routine antibiotics.
4. Wherever possible, micro-organisms should be cultured both aerobically and anaerobically and sensitivity to various anti-biotics established.
5. Metronidazole has a significant role in the treatment of anaerobic infections and in the prevention of these in the post-operative period, particularly with Bacteroides fragilis.
6. Metronidazole is well tolerated, and safe and therapeutically effective blood levels are rapidlyachieved by its intravenous use.

**Material and Methods**

The cases included in the trial were those met in general surgical practice, where anaerobic infection was suspected on clinical grounds. Presence of foul smelling pus, gas bubbles in the wound and poor

response of the infection to ordinary broad spectrum anti-biotics were the criteria used for selection of cases (Table I).

Table I

Criteria for Diagnosis of Anaerobic Infections

| *No.* | *Criterion* |
|---|---|
| 1. | The presence of profuse, thick foul smelling, purple color pus. |
| 2. | Gas bubbles in the infected area. |
| 3. | Extensive necrosis and induration in the local tissues. |
| 4. | Lack of response to ordinary broad spectrum antibiotics. |
| 5. | Abacterial pus on ordinary culture. |
| 6. | Favourable therapeutic response to Metronidazole. |
| 7. | Positive cultures for anaerobes. |

In some of these patients cultures were negative both for aerobes and anaerobes.
The analysis of cases included in the trial is shown in Table II.

## Table II Analysis of Cases

| No. | Diagnosis | No. of cases |
|---|---|---|
| 1. | Appendicectomies (gangrenous & perforated). | 18 |
| 2. | Strangulated Hernias. | 9 |
| 3. | Peritonitis following Typhoid perforations. | 6 |
| 4. | Gram Negative Septicemia. | 3 |
| 5. | Gas Gangrene. | 3 |
| 6. | Empyema thoracis. | 2 |
| 7. | Pulmonary infections following a stab wound not responding to routine antibiotics. | 2 |
| 8. | Multiple bullet injuries of abdomen with peritonitis. | 2 |
| 9. | Volvulous of Sigmoid Colon leading to gangrene. | 2 |
| 0. | Amoebic Colitis with perforation. | 2 |
| 1. | Subphrenic abscesses. | 1 |
| | Total: | 50 |

9 patients i.e., 18% needed a change of antibiotics after the receipt of culture and sensitivity report. All patients received Metronidazole in addition to other antibiotics as shown in Table III.

## Table III

### Antibiotics Used in Addition to Metronidazole

| *No.* | *Drugs* | *Diagnosis* |
|---|---|---|
| 1. | Ampicillin | Appendicectomies |
| 2. | Velosef | Strangulated Hernia |
| 3. | Chloramphenicol | Typhoid perforation |
| 4. | Genticin | Gm-Ve Septicemia |
| 5. | Penicillin | Gas Gangrene |
| 6. | Ampiclox | Chest infection, bullet injuries of abdomen. |

Metronidazole was used in standard doses of 500 mg, intravenously 8 hourly for a minimum period of 2 days and maximum 5 days. This was followed by oral administration. The decision to change to oral form was made on clinical grounds. Age variatior of the patients was 18-62 years. Sex incidence was 32 males and 18 females (Table IV, Fig. I).

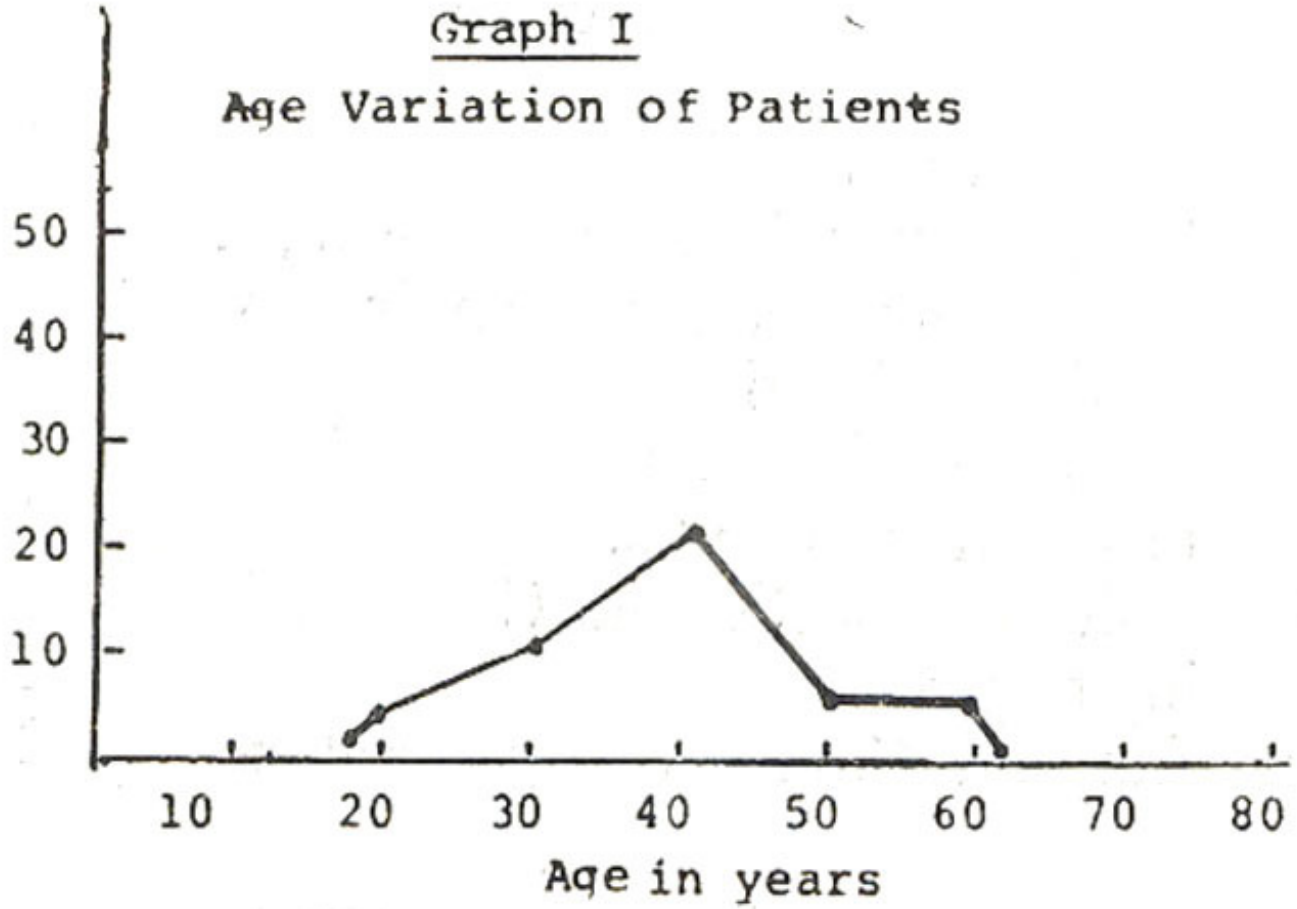



*Fig.* 1: Age Variation of Patients

Table IV

Age and Sex Distribution of the Patients

| Age Group | Male | Female | |
|---|---|---|---|
| 18—20 years | 2 | 2 | |
| 21—30 ,, | 9 | 2 | |
| 31—40 ,, | 15 | 8 | |
| 41—50 ,, | 3 | 3 | |
| 51—60 ,, | 2 | 3 | |
| 61—62 ,, | 1 | — | |
| Total: | 32 | 18 | Grand Total: 50 |

All the patients were carefully monitored for any adverse reactions. A four hourly temperature, pulse and blood pressure were recorded 4 hourly. Wound examination was performed on 2nd, 4th and 7th day in all patients and more frequently if needed. The patients data were checked regarding comfort of wound, edema, smell, induration and discharge. Any unpleasant side- efficts were recorded according to the pa-timt's statement. Repeated examination was done for any skin rashes, inco-ordination of movements furring of tongue or darkening of urine.

Cultures and sensitivity studies were carried cut in 42 patients both aerobically and anaerobi-cally. Fluid from the hernial sac or gangrenous bowel and pus were the materials used. In patients with septic shock, blood cultures were carried out The specimens were collected in tubes having Thioglycolate medium, and they were incubated for 48 hours. In cases where copious pus was available, the tube was completely filled and immediately transported to the lab. It was incubated for 48 hours for anaerobes at 3"/°C for study of anaerobes. Streaking was done on blood agar plates and incubated in Mcintosh Field's Jar. Colonies were further differentiated by using sugars and other chemical reagents. In the remaining cases diagnosis was made on clinical criteria already mentiened.

**Results**

Majority of patients showed a satisfactory response. 8 patients died during the trial due to severe toxemia and fulminating infection. Details are given in Table V.

## Table V Death Record

| *No.* | *Diagnosis* | *No. of Patients* | *Duration Post-operative* |
|---|---|---|---|
| 1. | Peritonitis with Typhoid perforations | 3 | 48—96 hours |
| 2. | Gram-ve Septicemia | 2 | 24 hours |
| 3. | Amebic Colitis with multiple perforations | 2 | 1st after 72 hours<br>2nd after 96 hours |
| 4. | Volvulous of sigmoid colon | 1 | 36 hours |
| | Total:- | 8 | |

Almost 50% of cases suffering from the fulminating infection like typhoid perforations, Gram-ve septicemia and gangrene of bowel could be saved by Metronidazole therapy. Whereas the previous such cases showed almost 70% mortality. The results of various bacteriological studies are given in Table VI and Fig. 2.

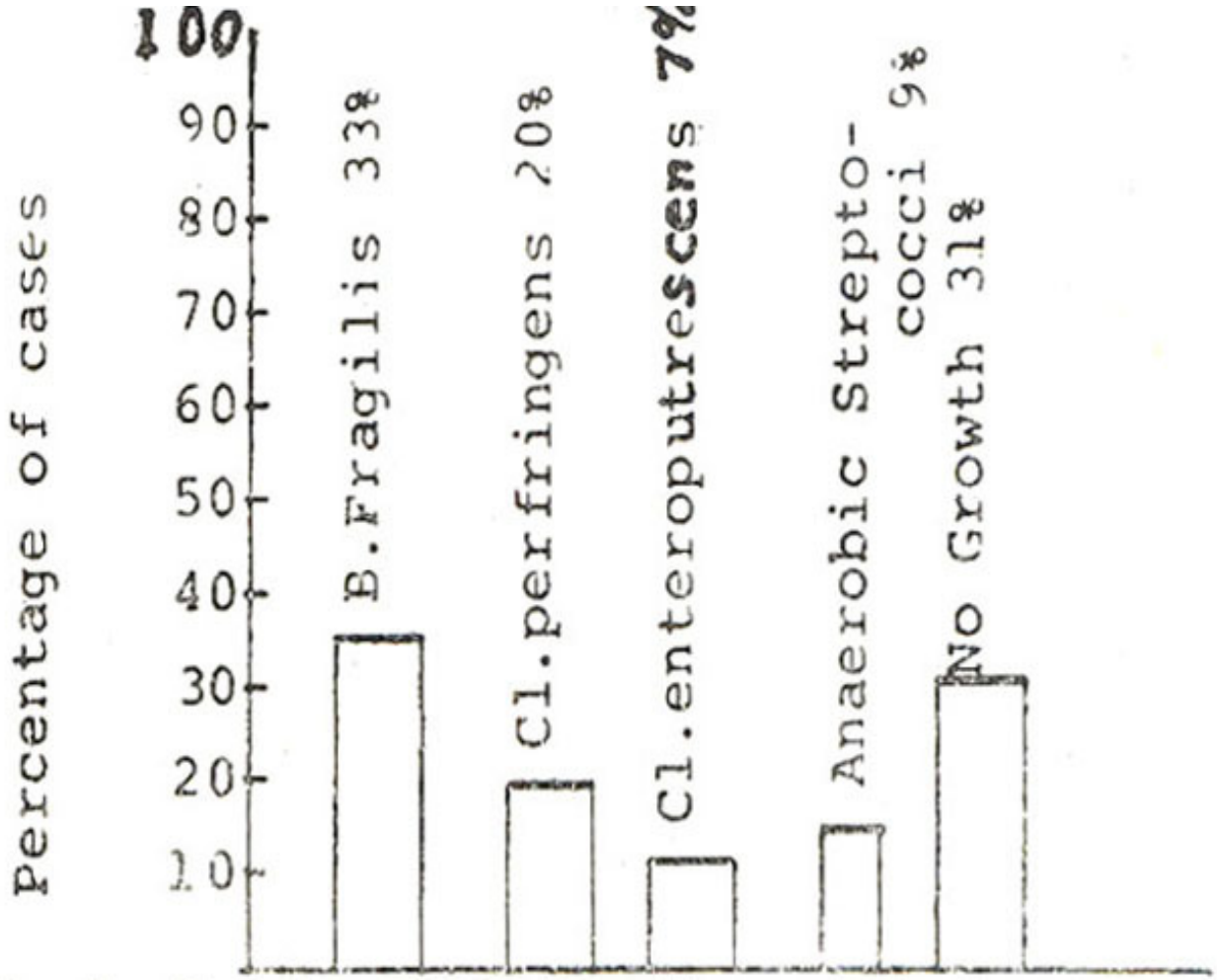



*Fig*. 2: Results of Various Bacteriological Studies

## Table VI

### Culture Studies

| *Aerobic Bacteria* | | *Anaerobic Bacteria* | |
|---|---|---|---|
| E. Coli | 21 | Bacteroides fragilis | 14 |
| Streptococcus pyogenus | 6 | Clostridia per fringens | 8 |
| Pseudomonas aeruginosa | 5 | Clostridia enteroputrescens | 3 |
| Klebsiella | 3 | Anaerobic streptococci | 4 |
| Streptococcus fecalis | 3 | No Growth | 13 |
| Staph. aureus | 2 | | |
| No growth | 2 | | |
| Total: | 42 | | 42 |

Therapeutic efficacy of the drug was assessed on the basis of the criteria as shown in table VII.

## Table VII

### Assessment of Efficacy

| *Response* | *Wound Infections* | *Temperature* | *Foul Smelling Discharge* |
|---|---|---|---|
| Good | Nil | Normal | Nil |
| Satisfactory | + | + | Nil |
| Poor | + | + | Present |

The results are graded in Table VIII and Figure 3.

8 patients complained of unpleasant taste in the mouth while 4 patients had upper G.I.T. upset. Only 2 patients developed a skin rash. In none of the patients the side-effects were so severe as to necessitate

stoppage of the therapy. All the side effects were transient.

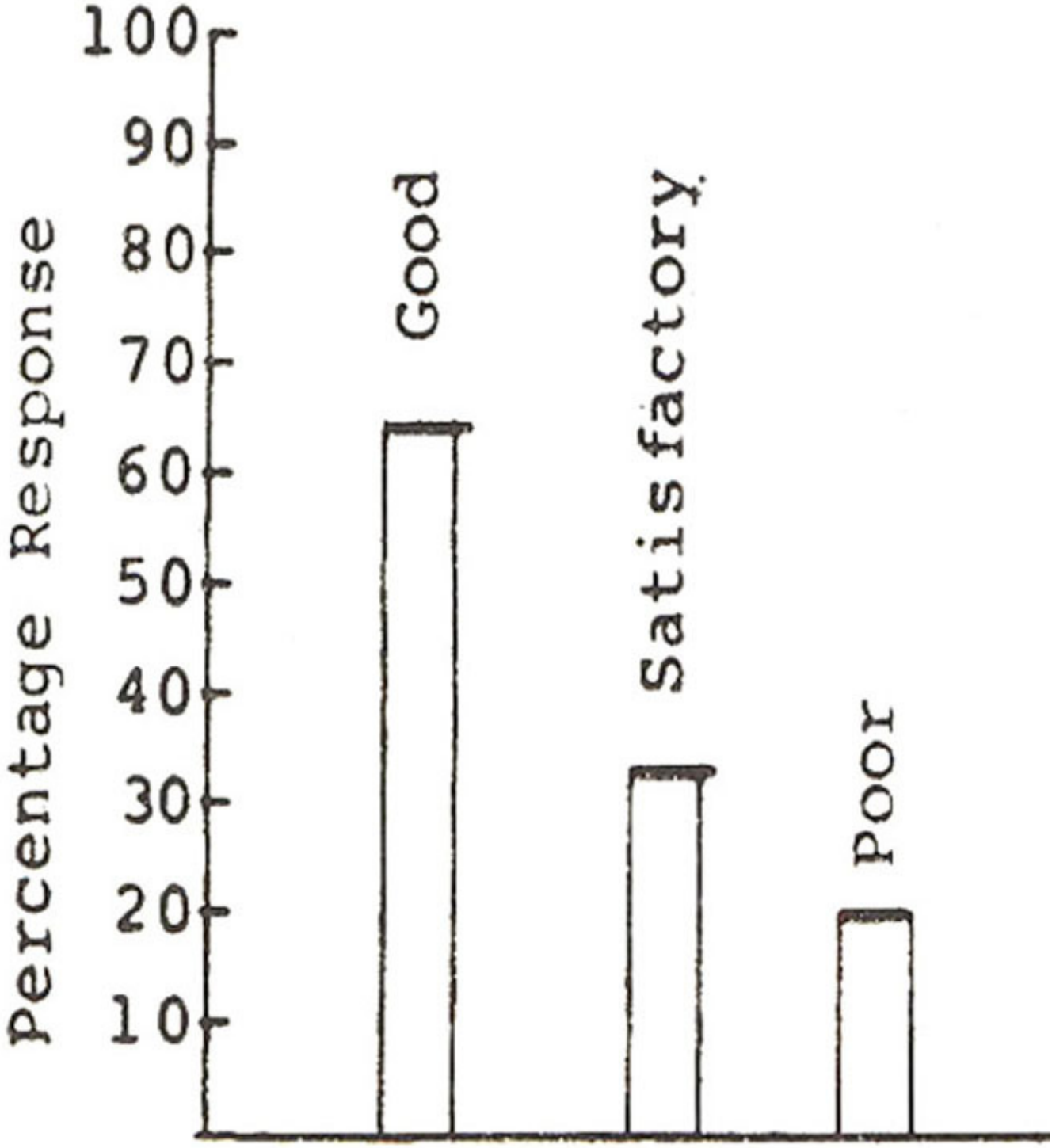



*Fig.* 3: Percentage Response

A comparative assessment of the clinical response to Metronidazole was done against results of similar operations in the past year in which only broad spectrum antibiotics were used.

# Table VIII

## Response Table

| *No.* | *Diagnosis* | *Good* | *Satisfactory* | *Poor* |
|---|---|---|---|---|
| 1. | Appendicitis | 15 | 2 | 1 |
| 2. | Strangulated Hernia | 6 | 2 | 1 |
| 3. | Typhoid perforations | — | 2 | 1 |
| 4. | Gram-ve Shock | — | 1 | — |
| 5. | Gas Gangrene with amputation | 1 | 2 | — |
| 6. | Empyema thoracis | — | 1 | 1 |
| 7. | Fulminating Pulm. Infection | 1 | 1 | 1 |
| 8. | Bullet Inj. Abdomen | 2 | — | — |
| 9. | Volvulous of Sigmoid Colon | 1 | — | — |
| 10. | Subphrenic abscess | — | 1 | — |
| | Total: | 26 | 12 | 4 |
| | Deaths: | 8 | | |
| | Grand Total: | 50 | | |

Table IX Comparative Analysis

| *A. AC. Appendicitis* | *Antibiotic Alone* | *Antibiotic + Metronidazole* |
|---|---|---|
| 1. Wound infection | 13/50—26% | 2/18—11.1% |
| 2. Fecal Fistula | 2/50— 4% | Nil |
| 3. Pelvis abscess | 2/50— 4% | Nil |
| 4. Subphrenic abscess | 1/50— 2% | — |
| *B. Strangulated Hernia* | *Antibiotic Alone* | *Antibiotic + Metronidazole* |
| 1. Wound infection | 3/10—30% | 1/9—11.1% |
| 2. Prolonged Ileus | 3/10—30% | Nil |

The comparative results are given in Table IX and percentage of wound infection is shown in Figure 4.

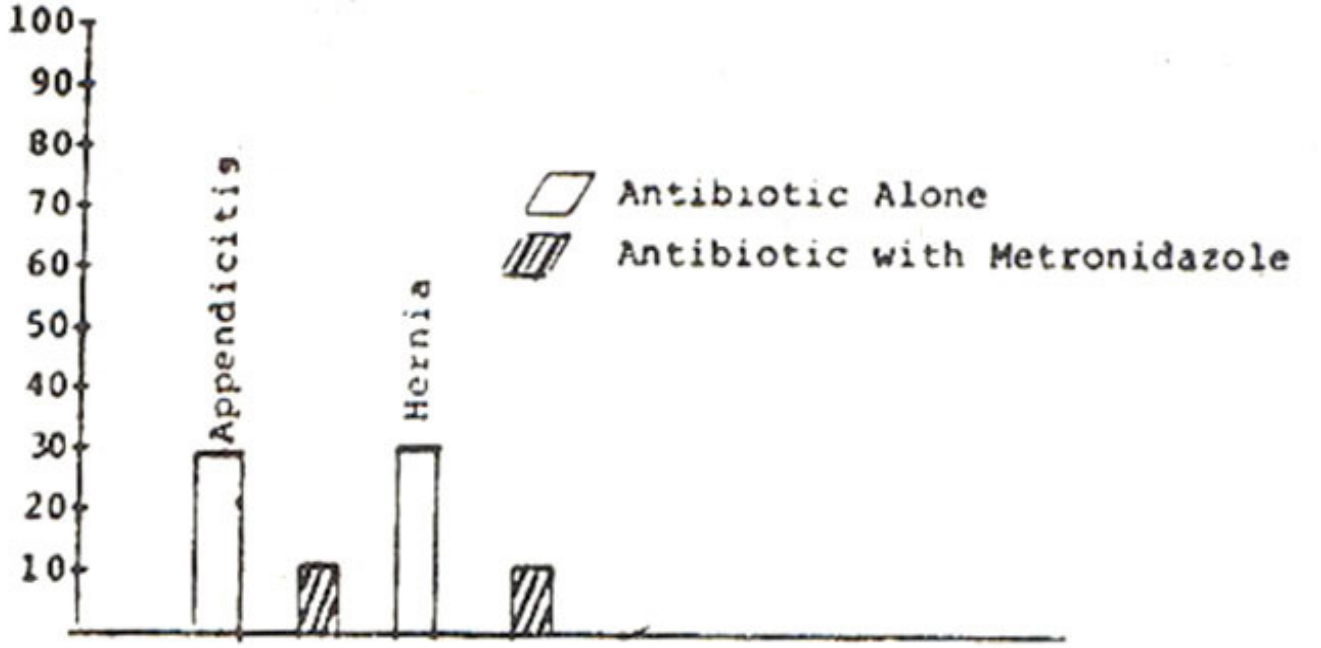



*Fig.* 4: Wound Infection Percentage

It is evident from the table that Metronidazole used in conjunction with broad spectrum drugs significantly reduces post operative complications and mortality.

## Discussion

Anaerobic bacteria have always been important pathogens for human infections. The recent rapid rise in the reported frequency of anaerobic infection over the last two decades is attributed to sophisticated techniques for the isolation of anaerobic bacteria combined with an increased awareness of their presence.

Anaerobic bacteria are the normal inhabitants of the intestine, urinary tract, female genital tract, upper respiratory tract and lungs (Lees and McNaught, 1959). They may get an entry into devitalised tissue and cause serious and occasionally fatal infections. They are also seen in many diverse surgical conditions like acute appendicitis,peritonitis due to gangrenous or perforated bowel, brain, lungs and liver abscesses, septic abortions and post operative wound and chest infections.

Early recognition and institution of appropriate therapy may help to avoid unnecessary complications. Out of various drugs like chloramphenicol, clindamycin, carbenicillin and tetracyclines, metronidazole stands out as the most effective and least toxic drug against anaerobes (Long et al., 1975).

Its availability as an intravenous preparation has further contributed towards its effective use in pre and immediate post operative period when oral therapy is not possible for obvious reasons. Gulaid et al. (1978) showed that higher concentrations in the range of 14 to 60 ug/ml are achieved at the end of intravenous infusion. The low incidence of serious side effects has made it a drug of choice against anaerobic infections. Since it is not effective against aerobes its use in combination with broad spectrum antibiotic is recommended.

The difficulty in isolation of anaerobic bacteria necessitates awareness of clinical criteria for diagnosing anaerobic infections. Metronidazole has an effective role in post operative management of acute surgical cases and has reduced the post operative complications in colonic surgery if used in bowel preparation (Taylor, 1979).

The difficulty in the isolation of anaerobic organisms necessitates that the anaerobic sepsis should be diagnosed clinically.

Metronidazole should be started on the fulfilment of the clinical criteria or when positive culture reports are available. It can also be used routinely in post operative management of acute appendicitis, peritonitis and large bowel surgery in conjunction with other broad-spectrum antibiotics to the advantage of the serious surgical cases.

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