Twenty-four Hour Preparation of the Large Bowel for Surgery Using Neomycin-Sulfathalidine or Neomycin-Oxytetracycline: A Comparative Evaluation *

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Introduction

THE status of colonic surgery has had a remarkable stimulus since 1940 when Devine stated that primary colectomy had a mortality of 30 per cent.[7] He advised that colostomy be performed whenever possible prior to the colectomy. Poth introduced Sulfathaladine in 1942, with a subsequent reduction in morbidity and mortality of colonic surgery.[10, 11] In 1950, Poth recommended Neomycin as the most effective intestinal antiseptic.[12] He subsequently found that Aerobacter organisms became resistant to Neomycin alone and advocated Neomycin and Sulfathalidine in combination to reduce these organisms.[6, 13, 15] More recently Neomycin has been combined with other newer wide-spectrum antibiotics in an attempt to further reduce the colonic flora.[1, 3, 6, 9, 16]

This study is an attempt to evaluate Neomycin-Sulfathalidine® and compare it with a combination of Neomycin and a wide-spectrum antibiotic, namely Neomycin-Oxytetracycline (Enterobiotic®). This has been done by bacteriologic and clinical means.

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Materials and Methods

Seventy-five patients about to undergo proposed colonic surgery were selected at random without regard to the operative procedure. Forty-two patients were given Neomycin-Sulfathalidine and 33 were given Neomycin-Oxytetracycline for bowel preparation. The surgeon did not know which drug combination was being used in the bowel preparation routine. The following routine was observed:

A cleansing tap water enema was given 24 hours preoperatively and stool specimens were taken for culture. The selected drug combination was then started and 60 cc. of castor oil were given for catharsis. No attempt was made to regulate diet but in most instances a low residue diet was prescribed. The Neomycin-Sulfathalidine combination was given as follows: Five tablets hourly for four doses, then five tablets every four hours for four more doses. Each dose contained one gram of Neomycin and 1.5 grams of Sulfathalidine. A total of 40 tablets containing eight grams of Neomycin and 12 grams of Sulfathalidine was administered to each patient.

The Neomycin-Oxytetracycline (Enterobiotic) combination was given at similar intervals but only four tablets were given. Each dose contained one gram of Neomycin and 200 mg. of Oxytetracycline. A total of 32 tablets containing eight grams of Neo-

mycin and 1.6 grams of Oxytetracycline was administered.

On the morning of operation another tap water enema was given and stool specimens were taken. Subsequent specimens were taken from the lumen of the bowel in 33 cases, either during operation or under sterile conditions immediately after operation from the surgical specimen. All patients received routine prophylactic antibiotics postoperatively, usually penicillin, 600,000 units twice daily and streptomycin, 0.5 gm. twice daily. Patients who gave a history of penicillin reactions were given tetracycline, either 500 mg. twice daily intravenously or 100 mg. intramuscularly every six hours.

Specimens, upon receipt at the laboratory, were either processed immediately or, if necessary, stored under refrigeration (4° C, − 20° C., or − 70° C.). At the time of processing, one gram of liquid, soft or firm stool was transferred with sterile saline to a sterile flask containing glass beads. The flask was shaken until a uniform suspension of the material was obtained and saline was added to obtain a total volume of 100 ml. If the specimens were entirely fluid, one ml. was transferred directly to nine ml. of saline for the initial preparation. Subsequently serial ten-fold dilutions were prepared from the material. Sterile 0.9 per cent saline was used routinely as the diluent. All pre-treatment specimens were pour-plated in five serial dilutions in the range of 10^{-3} to 10^{-9}. All post-treatment and surgical specimens were pour-plated in the lowest dilutions prepared. Azide blood agar * (2½ per cent blood bank blood) was used for the counts of Gram-positive cocci, MacConkey Agar * for coliforms and non-coliform Gram-negative bacilli, Anaerobic Agar * for *Clostridium* and facultative anaerobes and Littman Medium * with streptomycin or Mycophil Agar * at pH 4–4.5 for yeasts and yeast-like organisms. One ml. aliquots of the dilutions from the lowest to 10^{-8} for pre-treatment specimens and to 10^{-6} for post-treatment and surgical specimens were transferred to Thioglycollate broth.* These tubes were then heated at 80° C. for ten minutes to destroy all vegetative forms of micro-organisms. One ml. aliquots over the full range of dilutions were transferred to Trypticase Soy Broth * or Tryptose Phosphate Broth.** After incubation, smears were made and Gram-stained from all tubes showing turbidity. This procedure provided a total count as well as a check on the types of organisms appearing in the plating media. The plates for yeast counts were incubated at room temperature for five to eight days. All other media were incubated at 37° C. for two days except the anaerobic plates which were incubated anerobically at 37° C. in a Brewer jar for five to eight days. Counts for the following groups of organisms were obtained: Gram-positive cocci, including streptococci and staphylococci; lactose non-fermenting Gram-negative bacilli; coliforms; clostridia; anaerobic spores; yeasts and yeast-like organisms; and total broth counts.

After the incubation periods all plates were counted for the appropriate types of organisms. Anaerobic and aerobic spore counts were recorded as the highest saline dilution heated in thioglycollate broth which showed Gram-positive bacilli with or without spores. Total counts were recorded as the highest saline dilution in trypticase soy or tryptose phosphate broth showing turbidity. These latter counts were generally one or two dilutions higher than the counts from azide blood agar and MacConkey agar.

At the end of the study (12 months) the cases were separated into two groups according to the combination of drugs used. Average counts for pre-treatment, post-treatment and surgical specimens were then

* BBL products.

** Difco products.

determined for each of the types or groups of organisms which could be determined by the procedure employed.

Bacteriological Results

Figure 1 is a graphic representation of these results with the counts plotted in logarithmic units. Tables 1 and 2 show the actual average counts in numerical form. It can be seen that both combinations of drugs accomplished a significant reduction of the colonic bacterial flora. More than a 99 per cent reduction in count was obtained from the pre-treatment to post-treatment phase with the exception of spores. They were reduced 98 per cent by Neomycin-Oxytetracycline and 97 per cent by Neomycin-Sulfathalidine. The yeast flora were altered only slightly and appeared to consist primarily of *Candida* species and *Geotrichum* species.

In some studies by other workers the period of treatment has been for two or more days.[3, 13, 14, 15] This has frequently resulted in the predominant growth, after the inhibition of the sensitive organisms, of various resistant microbial groups, usually *Aerobacter, Pseudomonas, Proteus Micrococcus* and *Candida.* This study used a short period of treatment in order to avoid this occurrence. It is therefore interesting to note that of the residual Gram-negative bacterial flora surviving treatment with Neomycin-Oxytetracycline approximately 80 per cent were coliform and 20 per cent were noncoliform; whereas this group surviving treatment with Neomycin-Sulfathalidine was approximately 10 per cent coliforms and 90 per cent non-coliforms. The non-coliform Gram-negative bacilli remaining after treatment with both combinations were primarily of the genus *Pseudomonas* and secondarily of the genus *Proteus.*

Clinical Results

Either Neomycin-Sulfathalidine or Neomycin-Oxytetracycline drug combination

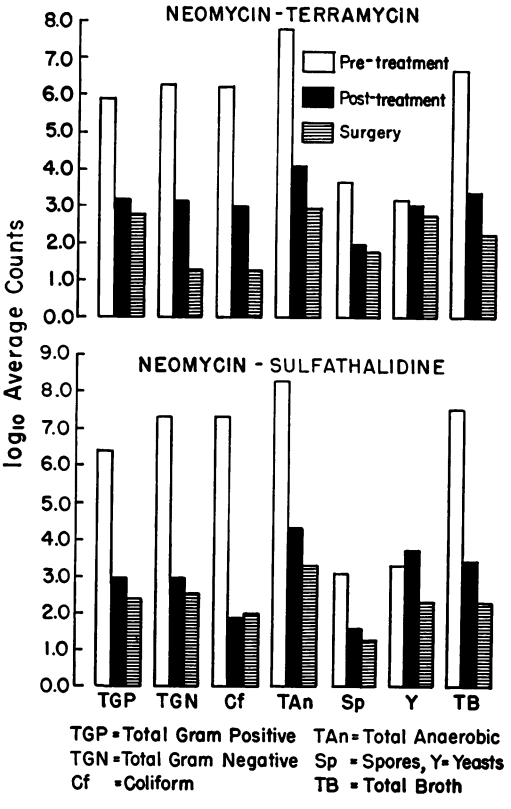

FIG. 1. Average logarithmic bacterial counts of pre-treatment, post-treatment, and surgical specimens using Neomycin-Sulfathalidine and Neomycin-Terramycin.

was administered to a total of seventy-five patients. Fifty-four patients actually had colonic surgery. A summary of the clinical course of these 54 patients is presented in Tables 3 and 4. Thirty-two patients were treated with Neomycin-Sulfathalidine and twenty-two with Neomycin-Oxytetracycline (Enterobiotic). It is interesting to note that only one wound infection occurred.

There were two anastomotic leaks, one of which resulted in the death of the patient from peritonitis on the sixteenth postoperative day following left colectomy. The other leak occurred in a 62-year-old man who had a left colectomy with a low anastomosis, This resulted in an abscess below the peritoneal reflection which slowly resolved but required a diverting colostomy.

Four deaths were recorded in this series.

TABLE 1. *Neomycin-Sulfathalidine*

Organism	Pre-Treatment Average Count*	Post-Treatment Average Count*	% Reduction	Surg. Specimen Count*
Total gram-positive	2,500,000	800	99	275
Total gram-negative	19,100,000	900	99	350
Coliform	18,900,000	70	99	95
Total anerobic	164,000,000	17,500	99	2,000
Spores	1,300	40	97	20
Yeasts	2,000	4,700	+236	200
Total	31,600,000	2,500	99	200

* Colonies per gram of feces or per ml. of liquid stool.

TABLE 2. *Neomycin-Terramycin*

Organism	Pre-Treatment Average Count*	Post-Treatment Average Count*	% Reduction	Surg. Specimen Count*
Total gram-positive	806,000	1,700	99	600
Total gram-negative	1,700,000	1,400	99	18
Coliform	1,650,000	1,100	99	18
Total anerobic	50,000,000	14,000	99	950
Spores	5,000	100	98	65
Yeasts	1,600	1,300	19	630
Total (broth)	5,000,000	2,500	99	200

* Colonies per gram of feces or per ml. of liquid stool.

One patient undergoing colostomy developed pneumonia and expired on the eleventh post-operative day. Another patient who had a left colectomy developed severe hypotension and bradycardia during operation and was comatose until death on the seventh postoperative day. An autopsy was not obtained but clinically the patient expired of cerebral damage. Prolonged ileus and distention caused the colostomy to withdraw into the peritoneal cavity in one patient on the twelfth postoperative day. He expired of multiple intra-abdominal abscesses and peritonitis on the thirty-first postoperative day. The last death occurred on the sixteenth postoperative day following an anastomotic leak in a patient having a left colectomy for diverticulitis. He had been placed on cortisone therapy previously for arthritis. Irrigations were given by error on the fourth and fifth post operative days into the distal loop of a transverse colostomy which had previously been performed for perforation of a diverticulum.

Discussion

The Gram-positive, Gram-negative, and coliform organisms were all reduced very effectively. The "Total Anaerobic" counts, which are greater than any of the other counts, include, in addition to the strictly anaerobic clostridia, many of the facultatively anerobic Gram-positive cocci, Gram-negative bacilli, and yeasts. If the sum of the post-treatment averages for these three groups are deducted from the post-treatment average total anaerobic counts, the remainder, presumably *Clostridium* species, is still larger than the post-treatment aver-

TABLE 3. *Summary of Clinical Results*

Neomycin-Sulfathalidine

Operation	No. of Cases	Average Highest Temp., °F.	Average Post-Op. Hospital Stay	Side Effects	Complications	Deaths
Colotomy	3	100^{2} (100–101)*	7 days (7 days)*	None	None	None
Rt. colectomy	3	100^{5} (99^{6}–100^{8})	11 days (11–12 days)	None	None	None
Lt. colectomy	12	100^{6} (99–103^{8})	12.2 days (7–18 days)	None	Ileus—1 Anastomotic leak—1 Wound infection—1 Hypotension and coma—1	Hypotension and coma—1 Peritonitis—1
Abdomino-perineal resection	9	101^{9} (99^{2}–103^{4})	27 days (12–48 days)	None	Urinary tract infection—1 Uremia—1 Stitch infection—1 Urinary retention—1 Colostomy withdrew—1	Peritonitis—1
Transverse colostomy or ileo-transverse colostomy	5	100.1 (99^{4}–101^{4})	7.7 days (7–10 days)	None	None	None
Colostomy	1	101	11	None	Pneumonia—1	Pneumonia—1

* Range.

ages for any of the other groups. This would seem to indicate that neither combination reduces the clostridial counts as effectively as the counts of the other groups. This is further borne out by the fact that the pre-treatment to post-treatment reductions of spores were less than the reductions with the other bacterial groups.

The increased average number of yeast organisms appearing after treatment with Neomycin-Sulfathalidine is difficult to interpret. This increase appears to be the result of two factors: a) Instances of undetectable numbers of yeasts (less than 100) before treatment and detectable numbers (greater than 10 or 100) after treatment; and b) a few instances of high numbers of yeasts (10^{-3} to 10^{-5}) before treatment and equally high numbers after treatment. Although the first factor would appear to indicate that the yeasts were developing after the bacterial flora had been inhibited, it is

TABLE 4. *Summary of Clinical Results*

Neomycin-Oxytetracycline

Operation	No. of Cases	Average Highest Temp., °F.	Average Post-Op. Hospital Stay	Side Effects	Complications	Deaths
Colotomy	4	100^{3} (100–100^{6})*	7.7 days (7–9 days)*	None	None	None
Rt. colectomy	2	99 (99^{2}–100^{2})	11 days (8–14 days)	None	None	None
Lt. colectomy	10	100^{3} (99^{2}–103^{6})	17 days (8–45 days)	None	Anastomotic leak—1	None
Abdomino-perineal resection	2	101^{5} (100–103)	42 days (32–52 days)	None	None	None
Transverse colostomy or ileocolostomy	4	100^{8} (100–100^{4})	19 days (7–36 days)	None	Thrombo-phlebitis—1	None

* Range.

questionable that a 2.4-fold increase in the average yeast counts would indicate a significant development of the yeast flora. Prigot *et al.*, without citing any specific figures, reported increased yeast counts after one- and two-day periods of treatment when neomycin was used alone or in combination with Erythromycin®, Carbomycin® or oxytetracycline.[16]

Absolute sterility of the colon was not accomplished in any case. In most cases the bacterial counts were markedly reduced, but growth of all organisms did occur to some extent. Three cases demonstrated bacterial counts that were approximately the same after the bowel preparation routine as before. These cases may be explained on the basis that colon obstruction was present in each instance. The drugs obviously did not reach the obstructed segment within the 24 hours of preparation in sufficient concentration to reduce the flora. This emphasizes that transverse colostomy is indicated if marked obstruction is present, followed by thorough irrigations of the distal loop. Instillation of the antibiotic combination may be done through the distal loop prior to final colectomy for further reduction of the bacterial count.

Pulaski *et al.* showed that mechanical cleansing of the bowel by catharsis and enemas in addition to a low residue diet will reduce certain flora to some extent but the total count is not affected.[17] Antibiotics which reduce colonic flora must be added to the regime.

On the basis of this study it appears that Neomycin in combination with either Sulfathalidine or Oxytetracycline offers consistently good reduction of colonic flora. There was no evidence of toxicity or significant side-effects using the recommended dosage for a 24 hour bowel preparation.

Summary and Conclusions

1. Seventy-five patients undergoing proposed colonic surgery in a one year period were studied bacteriologically and clinically to determine the efficacy of a 24 hour bowel preparation routine using Neomycin-Sulfathalidine and Neomycin-Oxytetracycline.

2. Colonic bacterial flora were reduced 99 per cent or better with both Neomycin-Sulfathalidine and Neomycin-Oxytetracycline drug combinations but absolute sterility was not obtained.

3. No overgrowth of yeast organisms noteworthy in longer bowel preparation routines occurred with 24 hour bowel preparation.

4. The only cases in which no reduction of colonic flora was obtained were patients with obstruction of the colon, emphasizing the importance of preparatory colostomy in these instances.

5. No adverse side effects were noted with either drug combination.

6. Neomycin-Sulfathalidine and Neomycin-Oxytetracycline, in the manner studied, were shown to be equally effective agents for reduction of colonic flora.

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