Original Articles

Double-blind trial of perioperative intravenous metronidazole prophylaxis for abdominal hysterectomy

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A double-blind trial of perioperative intravenous metronidazole treatment to prevent infections at the operative site and unexplained fever after abdominal hysterectomy was conducted in 106 patients. Metronidazole prophylaxis reduced the rate of recovery of anaerobes from vaginal swabs for several days and prolonged the high rate of vaginal carriage of enterococci and aerobic gram-negative bacilli following hysterectomy. Although the fever index, calculated from the duration of a temperature above 37.3°C, was significantly lower in the metronidazole-treated group than in the placebo-treated group, the frequency of postoperative infections, the proportion of patients requiring antibiotic treatment and the average duration of hospital stay were similar in the two groups. These results do not support the reported value of perioperative metronidazole prophylaxis in patients undergoing abdominal hysterectomy.

Une étude à double-insu du traitement intraveineux au métronidazole en période péri-opératoire pour la prévention des infections au site opératoire et des fièvres inexpliquées après l'hystérectomie abdominale a été menée chez 106 patientes. La prophylaxie au métronidazole a réduit la fréquence d'isolement des anaérobies par écouvillonnage vaginal et a prolongé le taux élevé de colonisation vaginale par les entérocoques et les bacilles gram-négatifs aérobies qui suit l'hystérectomie. Quoique l'indice de fièvre, calculé d'après la durée de température au dessus de 37.3°C, était significativement inférieur dans le groupe traité au métronidazole, la fréquence des infections post-opératoires, la proportion de patientes nécessitant une antibiothérapie et la durée moyenne du séjour à l'hôpital furent semblables dans les deux groupes. Ces résultats ne confirment pas la valeur rapportée de la prophylaxie au métronidazole en période péri-opératoire de l'hystérectomie abdominale.

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Perioperative antibiotic prophylaxis in gynecologic surgery is a contentious issue. The best antimicrobial agent or combination of agents and the best dosages remain unclear. Optimal antibiotic prophylaxis may differ with the type of gynecologic surgery, the patient population and the institution.

Increasing awareness of the role of anaerobic bacteria, principally *Bacteroides fragilis*, in postoperative infections in pelvic tissues and of the activity of metronidazole against these organisms[1] has led to studies of the efficacy of prophylaxis with this antibiotic in patients undergoing gynecologic surgery.[2-5] In three of these studies data from patients undergoing abdominal hysterectomy were combined with those from patients undergoing vaginal hysterectomy.[2,3,5] In the other study metronidazole was given for 24 to 48 hours before and for 7 days after elective abdominal hysterectomy.[4] To establish more precisely the efficacy and adverse effects of metronidazole in patients undergoing only abdominal hysterectomy we undertook a prospective, double-blind, placebo-controlled study of perioperative prophylaxis with three intravenous doses of metronidazole. We considered prevention of infection at the operative site and in contiguous pelvic tissues and reduction of the frequency of unexplained fever requiring antibiotic therapy to be important clinical indices of drug efficacy. In addition, we compared the effects of metronidazole and a placebo on a number of other relevant clinical and microbiologic parameters.

Material and methods

Patients and treatment

We considered 216 patients consecutively admitted to hospital for elective abdominal hysterectomy for enrolment in the study (which had been approved by the clinical trials committee of the Montreal General Hospital) but excluded 19 because of thyroid disease, antibiotic treatment in the preceding 2 weeks, pelvic inflammatory disease, pregnancy or their physician's preference for antibiotic prophylaxis; 89 patients declined to take part. The remaining 108 patients signed an informed consent form and were randomly assigned to receive either metronidazole (500 mg in 100 ml of normal saline) or a placebo (100 ml of normal saline) infused intravenously over 20 minutes every 6 hours for

three doses, starting when the patient was called to the operating room. The data for two patients were excluded before the code was broken, in one instance because hysterectomy was not performed, though a laparotomy was, and in the other because the protocol for administration of the drug was not followed; neither patient had an unexplained fever or an adverse drug reaction, and the one in whom hysterectomy was performed did not have an infection of the operative site. The treatment groups were compared for age, weight, previous metronidazole treatment, frequency of abnormal laboratory data, underlying disease, indication for hysterectomy, vaginal and cervical flora, and surgical procedure.

Assessment

A double-blind clinical evaluation was performed. A fever index[6] was computed by multiplying the area below the temperature curve but above the baseline of 37.3°C by the number of hours the fever persisted; 0.5°C was subtracted from rectal temperatures. Vaginal cuff abscess was diagnosed from the presence of fever, abnormal pain and tenderness, and a mass demonstrable clinically and radiologically (by radioisotopic or ultrasonographic examination), whereas pelvic cellulitis was diagnosed from the presence of fever, abnormal pain and abnormal results of a pelvic examination but no demonstrable mass. Purulent discharge from the abdominal wound was considered to indicate infection; the infection was classified as minor if the wound was 2 cm or less in length, moderate if the wound was longer but the infection did not require treatment and severe if the wound was longer and the infection required treatment. "Standard febrile morbidity" was defined as an oral temperature of 38°C or more on 2 postoperative days, excluding the first, without any signs of infection.

Pneumonia was diagnosed by the presence of fever, cough, rales and radiologic evidence of infiltration. Urinary tract infection was diagnosed when at least 100 000 colony-forming units of a bacterium were cultured per millilitre of a sample from a Foley catheter or two samples of clean voided urine.

The impact of metronidazole prophylaxis on the patient was assessed by the length of hospital stay specifically required for management of problems directly or indirectly related to the hysterectomy and related treatment. An antibiotic "course" was defined as any regimen lasting more than 48 hours. The patient was asked each day about subjective adverse reactions with the aid of a standard question list. Objective adverse reactions included new signs detected by physical examination that could possibly be related to drug administration.

In most cases a vaginal and a cervical sample were taken for culture before the operation, and a vaginal sample was taken 3.9 ± 1.4 days (mean ± standard deviation [SD]) after the hysterectomy. In 53 cases another vaginal sample was taken 5 or more days after the operation (mean ± SD, 6.4 ± 1.5 days). Each sample consisted of two swabs, one transported in Stuart transport medium, the other in thioglycollate. Both were inoculated within 2 hours of sampling on *Brucella* agar supplemented with vitamin K and hemin, with or without neomycin, the plates being incubated anaerobically, and on MacConkey and blood agar plates, which were incubated aerobically. An adverse microbiologic effect was defined as a nosocomial infection due to an organism recovered in the vaginal flora after the operation that had not been present preoperatively.

Six weeks after discharge the patients were contacted by telephone or mail to report late complications.

Statistical analysis

Age, weight and fever index were compared by two-tailed *t*-tests, differences in proportions were analysed by the chi-square test, and the duration of symptoms and the number of antibiotic courses were compared by the Mann–Whitney U-test. $P < 0.05$ was considered to represent a significant difference.

Results

The two groups did not differ in age, weight, frequency of previous metronidazole therapy, distribution of indications for the operation or distribution of surgical procedures performed (Tables I and II). The hemoglobin level was low in 27 of the 49 patients tested in the metronidazole group and in 17 of the 49 patients tested in the placebo group (not a significant difference). The proportions with abnormalities in the leukocyte count, the levels of glucose and urea in the blood, and the results of liver function tests, urinalysis and urine culture were similar in the two groups. Fourteen metronidazole-treated and 16 placebo-treated patients reported various diseases unrelated to the hysterectomy; 2 and 7 patients respectively reported high blood pressure

Table I—Characteristics* of patients before abdominal hysterectomy and prophylaxis with metronidazole or placebo

Variable	Metronidazole group (n = 53)	Placebo group (n = 53)
Age, yr (mean ± standard deviation [SD])	41.9 ± 8.7	44.1 ± 9.6
Weight, kg (mean ± SD)	62.8 ± 9.4	61.7 ± 11.5
Previous metronidazole treatment, no. of patients	4	2

*No differences between the groups were significant.

Table II—Indication for hysterectomy, and other surgical procedures undertaken*

Variable	No. of patients	
	Metronidazole group	Placebo group
Indication		
Bleeding, fibroids or endometriosis	33	35
Neoplasm	4	5
Incontinence or prolapse	4	3
Other or combination of the above	10	7
Not stated	2	3
Other surgical procedures		
Salpingectomy and/or oophorectomy	19	25
Vaginal repair and/or Marshall–Marchetti operation	5	1
Combination of the above	5	4
Other	7	5
None	17	18

*No differences between the groups were significant.

(not a significant difference). The preoperative vaginal and cervical flora were similar in the two groups (Table III).

The frequency of postoperative infection and standard febrile morbidity is shown in Table IV. One patient in the metronidazole group had a normal hospital course but was treated for vaginal vault induration, pain and discharge considered to be due to a vaginal vault infection. One patient in the placebo group had a pelvic abscess due to *Bacteroides* and anaerobic cocci. Of the abdominal wound infections all but four were minor; there were two severe infections in the metronidazole group, both caused by *Staphylococcus aureus*, and two severe infections in the placebo group, one caused by *Bacteroides* and the other by β-hemolytic *Streptococcus* not of Lancefield group A, B, C, D or G. Two patients in the metronidazole group were treated for symptoms of urinary tract infection after discharge from hospital: the culture results were negative in one, who may have had a urethral syndrome; cultures were not performed in the other. In the placebo group one patient had both a bacteriologically proven urinary tract infection and radiologically proven pneumonia, and another patient had vaginitis of unknown cause after discharge from hospital.

Standard febrile morbidity resolved without antibiotic therapy in six patients but required treatment in three (one in the metronidazole group and two in the placebo group). Three other patients (two in the metronidazole group and one in the placebo group) were given antibiotic treatment by their attending physician even though their fever did not conform to the definition of standard febrile morbidity.

Thus, infection of the pelvis, vaginal vault or abdominal wound, or standard febrile morbidity, developed in 10 (19%) of the 53 patients in the metronidazole group and 13 (24%) of the 53 in the placebo group.

The only statistically significant benefit ($P = 0.02$) of metronidazole in terms of morbidity was a reduction of 10.2 degree-hours in the fever index. Metronidazole treatment did not shorten the hospital stay or reduce either the frequency of antibiotic treatment or the total number of antibiotic courses given (Table V).

The frequency and duration of subjective adverse reactions were similar in the two groups except for headache, which had a significantly shorter ($P = 0.02$) reported duration in the metronidazole group. The frequency of objective adverse reactions that could possibly be attributed to the drug also did not differ between the two groups: after metronidazole prophylaxis a localized rash occurred in three patients, herpes labialis in two patients and superficial thrombophlebitis, tremor, and numbness over the lateral side of the thigh in one patient each. After placebo treatment superficial thrombophlebitis, herpes labialis, neurodermatitis and hypotension in the recovery room occurred in one patient each.

In both treatment groups the rates of recovery of enterococci and coliforms from the vagina were significantly greater ($P < 0.01$) after hysterectomy (Table VI). The differences were still significant 5 or more days after the operation in the metronidazole group but not in the control group. After metronidazole prophylaxis the rates of recovery of anaerobic cocci and aerobic streptococci other than β-hemolytic streptococci and enterococci were significantly reduced ($P < 0.05$). Postoperatively *Bacteroides* was cultured significantly less frequently ($P < 0.01$) in the metronidazole group than in the placebo group. The significant reduction in recovery rate persisted 5 days after the operation for the anaerobic cocci, but with the reduced number of patients tested the difference was no longer significant for *Bacteroides*. A significant reduction in the rate of recovery of lactobacilli was observed after placebo but not after metronidazole treatment. Microbiologic adverse reactions were demonstrated in four patients, three in the metronidazole group (two major *S. aureus* wound infections and one *Escherichia coli* urinary tract infection) and one in the placebo group (an *E. coli* urinary tract infection).

Table III—Preoperative genital flora*

Organism(s)	Frequency of recovery, % (and no. of patients tested)			
	Vagina		Cervix	
	Metronidazole group (51)	Placebo group (49)	Metronidazole group (51)	Placebo group (50)
Staphylococcus aureus	4	0	2	0
S. epidermidis	47	43	35	32
Beta-hemolytic streptococci	4	8	2	8
Enterococci	27	16	22	16
Other streptococci	16	16	14	10
Lactobacilli	75	82	69	68
Coliforms	16	20	6	14
Candida	10	6	8	6
Bacteroides	16	12	14	12
Anaerobic cocci	27	14	20	8

*No differences between the groups were significant.

Table IV—Postoperative infection and standard febrile morbidity

Postoperative problem	Metronidazole group	Placebo group
Infection, no. (and %) of patients		
Pelvic or vaginal vault	1 (2)	1 (2)
Abdominal wound	6 (11)	6 (11)
Urinary tract	6 (11)	6 (11)*
Other	2 (4)	2 (4)*
Standard febrile morbidity, no. (and %) of patients	3 (6)	6 (11)
Fever index[6] (mean ± SD)	13.5 ± 14.3	23.7 ± 31.4†

*One patient had both pneumonia and urinary tract infection.
†Significantly higher ($t = 2.152$, $P < 0.05$).

Table V—Impact of prophylaxis on the patients*

Variable	Metronidazole group	Placebo group
Length of hospital stay, d (mean ± SD)	7.2 ± 3.0	7.0 ± 3.2
Antibiotic treatment, no. (and %) of patients	14 (26)	14 (26)
Antibiotic courses, total no.	15	22
Objective adverse reactions, no. of patients	8	4

*No differences between the groups were significant.

Discussion

Perioperative intravenous administration of metronidazole failed to prevent infection at the operative site or postoperative fever requiring antimicrobial treatment. Pelvic or vaginal vault infection, major abdominal wound infection or standard febrile morbidity requiring treatment with antibiotics — the complications we wanted to prevent — occurred in 8% of the metronidazole-treated patients and 9% of the placebo-treated patients. (Because the differences between the treatment groups were so small, we did not discuss type II error [wrongly accepting the null hypothesis] in our analysis.) We do not believe that minor wound infections and standard febrile morbidity that resolve spontaneously justify antibiotic prophylaxis. The reduction of 10.2 degree-hours in the fever index, although statistically significant, is probably not clinically important and does not justify antibiotic prophylaxis. This interpretation is further supported by our inability to demonstrate any difference in length of hospital stay or in number of patients receiving antibiotics.

Our results contrast with those of Appelbaum and collaborators,[4] who observed a significant reduction, from 50% to 15%, in the frequency of vaginal vault or wound infection after abdominal hysterectomy. However, in that series of patients most infections resolved spontaneously, and the prophylactic regimen was continued for 7 days after the operation. Jackson and associates[5] reported a significant reduction in the fever index, 12.9 degree-hours, after abdominal hysterectomy in a group of patients given a metronidazole suppository perioperatively. They also reported a rate of pelvic or wound infection of 1% after metronidazole treatment and 18% after placebo treatment, but they did not separate infections following abdominal hysterectomy from those following various vaginal operations. Stocklund and colleagues[7] reported a slight but not statistically significant reduction in the infection rate after abdominal hysterectomy in patients given prophylaxis with ornidazole (another nitroimidazole antibiotic). The low frequency of infection did not appear to justify antibiotic prophylaxis in their study.

Table VI—Postoperative vaginal flora

Organism(s)	Postoperative culture; frequency of recovery, %* (and no. of patients tested)			
	First, 3.9 ± 1.4 d (mean ± SD) after hysterectomy		Last, 5 or more d (mean ± SD, 6.4 ± 1.5) after hysterectomy	
	Metronidazole group (47)	Placebo group (45)	Metronidazole group (27)	Placebo group (26)
S. aureus	11	5	11	4
S. epidermidis	43	37	41	46
Beta-hemolytic streptococci	2	4	4	4
Enterococci	59†	44†	56†	35
Other streptococci	2‡	9	7	4
Lactobacilli	63	49†	59	62
Coliforms	54†	47†	67†§	35§
Candida	2	11	15	8
Bacteroides	4§	22§	4	15
Anaerobic cocci	9‡	18	7‡	31

*Significantly different from the preoperative rate at $P < \dagger 0.01$ and $\ddagger 0.05$, and §significantly different from the postoperative rate in the other treatment group ($P < 0.05$).

Prophylactic administration of β-lactam antibiotics (e.g., penicillins and cephalosporins), either in a prolonged regimen[8,9] or perioperatively,[10,11] has reduced the frequency of infection at the operative site and unexplained fever after abdominal hysterectomy. On the other hand, Grossman and coworkers[12] failed to demonstrate such a protective effect, and Ohm and Galask[13] observed a reduction in the frequency of infections at the operative site but an increase in the frequency of unexplained fever. Beta-lactam antibiotic prophylaxis can reduce the frequency of urinary tract infection, but this is not a primary objective of antimicrobial prophylaxis, as such an infection is easily detected by urine smear and culture. Furthermore, patients with prolonged bladder catheterization may be at a higher risk of infection with resistant bacteria if prophylactic antibiotics are given for several days.[14]

In our patients the perioperative intravenous use of metronidazole was well tolerated. No subjective side effects could be attributed to the drug; on the contrary, headaches were briefer after metronidazole prophylaxis. The frequency of objective adverse reactions did not differ from that in the control group.

This form of prophylaxis had a remarkable impact on the vaginal flora. A reduced frequency of recovery of anaerobes has been reported with prolonged metronidazole prophylaxis,[2,4] but we are the first to describe a similar effect with a short perioperative course. We also demonstrated a reduction in the rate of colonization of the vagina with non-β-hemolytic streptococci other than enterococci after metronidazole treatment. Two of the five patients with *S. aureus* colonization after metronidazole prophylaxis had a major staphylococcal infection, and we considered this an important adverse microbiologic effect of the drug. Our study confirmed the increased rate of recovery of aerobic gram-negative bacilli and enterococci after hysterectomy.[15] These changes in flora persisted longer in the patients who received metronidazole. The risk associated with such a change is not known, but Ti and collaborators have observed a higher frequency of urinary tract infection following perioperative intravenous metronidazole prophylaxis for vaginal hysterectomy (personal communication, 1981).

Our findings did not demonstrate a clinically important effect of perioperative intravenous metronidazole prophylaxis for patients undergoing abdominal hysterectomy in our institution. Thus, favourable reports[2-5] on the efficacy of prophylactic metronidazole should be interpreted cautiously. Discrepancies may arise from the heterogeneity of gynecologic operations in some of these studies and from the failure to distinguish between major infectious complications and minor postoperative infections that do not require antibiotic treatment and would not justify antibiotic prophylaxis.

We thank the personnel, house staff and members of the department of obstetrics and gynecology of the Montreal General Hospital for their collaboration. We are grateful to Dr. John Kreeft and Mrs. Emoeke Corwin for assistance in the statistical analysis and to Mr. Olu Marcus-Jones for the microbiologic analyses.

This study was supported by a fellowship award from the Medical Research Council of Canada to Dr. Vincelette and by a grant from Rhône-Poulenc Pharma Inc.

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Fragile X chromosome and X-linked mental retardation

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A family is described in which three normal females transmitted to seven males X-linked mental retardation associated with macro-orchidism and a fragile site on the long arm of the X chromosome — fra(X)(q27). The affected males also had minor clinical features in common: a large forehead, long face, large ears, a long upper lip and large extremities.

On décrit une famille où trois femmes normales ont transmis à sept de leurs enfants mâles une arriération mentale liée au sexe et associée à une macro-orchidie et à un site fragile sur le bras long du chromosome X — fra(X)(q27). Les mâles atteints présentaient aussi des caractéristiques cliniques mineures communes: un front large, un visage allongé, de grandes oreilles, une lèvre supérieure allongée et de grosses extrémités.

Twenty years ago in this Journal Renpenning and associates[1] described a large family from the Prairies in which mental retardation without physical abnormality was confined to males and transmitted by females over three generations. Since then many cases of X-linked mental retardation, macro-orchidism and an X-chromosome marker have been observed, either separately[2-7] or in association.[8-14] We present seven new cases from a single French Canadian family. All the affected individuals had confirmed mental deficiency, macro-orchidism and fragile X chromosomes. They also exhibited facial characteristics that may be part of this syndrome.

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Patients and methods

Seven mentally retarded young men and boys and three obligatory adult female carriers were studied clinically and by cytogenetic analysis. The relevant portion of their family tree is illustrated in Fig. 1. The

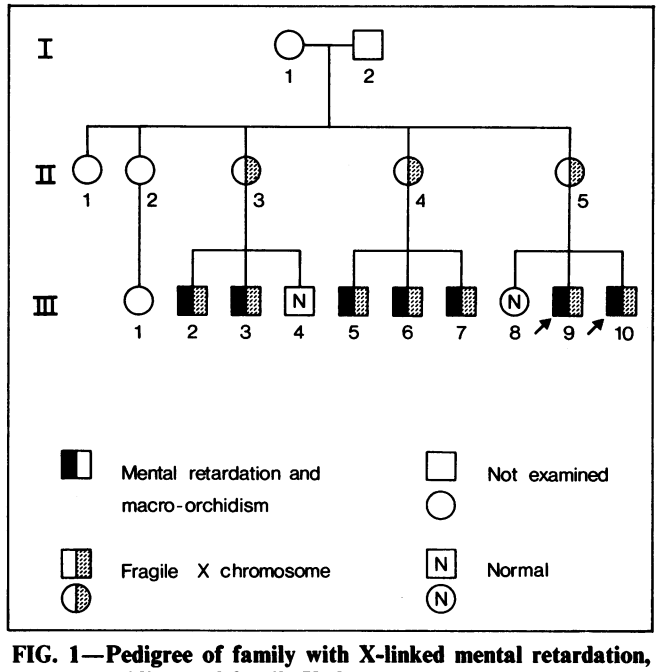

FIG. 1—Pedigree of family with X-linked mental retardation, macro-orchidism and fragile X chromosome.